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Title

Fruit intake reduces the onset of respiratory allergic symptoms in schoolchildren

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Running title: Fruit intake reduces respiratory allergy

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Fruit Intake Reduces the Onset of Respiratory Allergic Symptoms in
Schoolchildren

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Abstract

Background: Previous studies have shown that dietary pattern is associated with allergy prevention.

Methods: We conducted a prospective cohort study on all primary schools in Omihachiman City, Shiga Prefecture, Japan. Questionnaires regarding allergic symptoms and diet were distributed to the parents of all 759 7-year-old schoolchildren for 4 consecutive years, from 2011–2014. Specific immunoglobulin E to inhalant allergens were measured at 10 years of age. Participants were then

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categorized as low, medium, or high intake during the study period for four food groups (fruits, vegetables, fish and beans). Logistic regression analysis was performed to estimate odds ratios and 95% confidence intervals.

Results: A total of 520 children (68.5%) whose parents responded to the questionnaires all 4 years were included in the analysis. The prevalence of asthma, rhinitis, and any allergic symptoms at age 10 was significantly decreased with increases in fruit intake. In addition, the onset of any allergic symptoms during the study period was significantly decreased with increases in fruit intake (33.3%, 28.3%, and 14.3% in children with low, medium, and high fruit intake, respectively; P for trend = 0.01). The sensitization rate to ragweed at age 10 was significantly decreased with increases in fruit intake (P for trend = 0.046). No significant effect was observed for the other three food groups, except for the association between fish intake and new onset asthma symptoms.

Conclusions: These findings suggest that higher intake of fruit can help prevent respiratory allergic symptoms in schoolchildren.

Keywords: allergen sensitization; childhood; diet; epidemiology; food intake

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Introduction

Because the prevalence of allergic diseases has recently been on the rise (1), early intervention strategies to prevent the onset of allergic symptoms should be considered. Several previous studies have shown that dietary pattern is associated with allergy prevention. For example, the Mediterranean diet, which involves relatively high consumption of fruit, vegetables, beans and fish, and relatively low consumption of meat and dairy products, has been shown to help prevent asthmatic symptoms in children (2, 3). The cause of this effect is considered to be the abundance of antioxidants, such as vitamins C and E, polyphenols, and carotenoid, as well as high *n*-3 and low *n*-6 unsaturated fatty acids, in such diets (4), as diets high in antioxidants have been shown to prevent allergy symptoms through their anti-inflammatory effects (5). In addition, such diets have been reported to affect the intestinal microflora, which may indirectly lead to the suppression of allergic diseases (6). Several reports have shown that dietary patterns, as opposed to individual ingredients, are important for allergy prevention (7–9). Dietary intervention might therefore be important from early infancy, or even during pregnancy (10–13).

Only a few previous investigations have been conducted using longitudinal surveys (14–16), and a causal relationship between diet and allergy has yet to be confirmed. Moreover, several studies have reported finding no allergy-preventive effects as a result of diet (17, 18). To prospectively investigate the association between diet and allergic symptoms, we used data collected in our recently performed 4-year longitudinal survey investigating the effect of various lifestyle

factors on allergic symptoms, the Lifestyle and Allergy among Kids in Elementary school (LAKE) study (19) to examine the effects of four supposedly allergy-suppressive foods (2, 3)—fruits, vegetables, fish and beans—on allergic symptoms in schoolchildren.

Methods

We conducted a prospective cohort study involving every primary school in Omihachiman city, Shiga Prefecture, Japan in 2011. Questionnaires regarding allergic symptoms (ISAAC; International Study of Asthma and Allergies in Childhood) and diet (BDHQ; brief self-administered diet history questionnaire) were distributed to the parents of all 7-year-old schoolchildren for 4 consecutive years, until 2014, when the children were 10 years old. Blood samples were obtained from the children in September 2014, and levels of immunoglobulin E (IgE) specific to four inhalant allergens (house dust mites, Japanese cedar, orchard grass and ragweed) were measured using ImmunoCAP (Phadia, Uppsala, Sweden). Levels of 0.7 UA/mL or higher were considered positive.

The BDHQ is a brief, semiquantitative, and comprehensive diet history questionnaire that assesses dietary habits during the preceding month. Estimates of daily food intake were calculated using an *ad hoc* computer algorithm based on standard food composition tables in Japan (20). Specifically, the amount of intake was calculated by multiplying sex- and age-specific portion sizes by the frequency of intake (21). The BDHQ was initially validated in adults before being modified for dietary assessment in children (BDHQ-10y) (22). The

BDHQ-10y comprises 54 food items in view of the legibility and knowledge of food. The intake of these 54 food items and 99 nutrients can then be calculated. The intake of 11 vegetable items is categorized into two groups: the sum of carrots/pumpkins, dark green vegetables, and tomatoes in one group (green-yellow vegetable group), and others. Fruit intake is the sum of three items: citrus fruits, Japanese persimmons, and strawberries, and others. Bean intake is the sum of three soy products: tofu (soybean curd), *natto* (fermented soybeans), and *miso* (fermented soybean-paste soup). The intake of nine fish items is categorized into three groups: dried and oily fish, total fish (small fish with bones, canned tuna, and lean fish), and total seafood (squid, octopus, shrimp, and shellfish). Nutrient and food intake is reported in terms of energy density (per 1,000 kcal). Parents were asked to answer each question along with their children. The exact questions regarding fruit intake are shown in Supplementary Data 1.

This study was approved by the Ethics Committee at the Kyoto University Graduate School of Medicine (E939). The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Parental response to the questionnaires was taken as informed consent from the parents.

Definition of allergic symptoms

Asthma, rhinitis, and eczema symptoms were estimated based on positive answers to the ISAAC questionnaires, in accordance with previous studies (19, 23). The exact definition of allergic symptoms is shown in Supplementary Data 2. “Any allergic symptom” was estimated based on the existence of any of these three symptoms. New onset symptoms were defined as symptoms that started only during the study period. Recovered symptoms were defined as symptoms that existed at the start of the study and disappeared by the end of the study.

Regarding food avoidance, we asked whether the children had ever avoided any foods due to allergic symptoms, and, if so, the kinds of foods and the duration of avoidance.

Definition of amount of food intake

For each food, participants were classified in order from the smallest to the largest intake and then divided into quarters in each year. Children classified in the third quartile or higher every year and in the fourth quartile in at least 3 of the years were defined as the high intake group, whereas those ranked in the second quartile or lower every year and in the first quartile in at least 3 of the years were defined as the low intake group. Participants fitting neither of these descriptions were defined as the medium intake group.

Statistical analysis

All analyzed data were categorical variables and are presented as number and percentage. We used the chi-square test to compare the characteristics of the participants, and then developed logistic regression models to estimate odds ratios (ORs), 95% confidence intervals (CIs), and P for trend. The primary outcome was the onset and recovery of allergic symptoms, and the secondary outcome was the prevalence of allergic symptoms and sensitization to inhalant allergens at 10 years of age. The exposure variable was the intake of fruit, vegetables, fish or beans during the study period. We included sex, season of birth, low birth weight (< 2500 g), birth order (first born), parent's allergies (presence of any allergic disease in either of the parents), breastfeeding (being completely breastfed for 6 months or more in infancy) and experience of food avoidance as confounders. We used penalized maximum likelihood logistic regression analysis to examine these variables (24). STATA/SE version 14.2 software (STATA Corporation, College Station, TX, USA) was used for statistical analyses. Statistical significance was set at two-tailed $P < 0.05$.

Results

Questionnaires were received from 667 of the 759 eligible children (response rate, 87.9%) in the first year of the study. Of these, the parents of 520 children (78.0% of those initially answered, 68.5% of total) provided answers to both the ISAAC and the BDHQ-10yr questionnaires for each year of the study period. Data from these 520 children were analyzed in the present study. The background

characteristics of the 520 enrolled children and the 147 unenrolled children are shown in Table 1. No statistical differences were found in the frequencies of these characteristics between the two groups except for allergic symptoms in the parents. The amount of food intake according to age is shown in Table 2.

Amount of food intake and allergic symptoms at 10 years of age

At 10 years of age, the prevalence of asthma symptoms (P for trend = 0.003), rhinitis symptoms (P for trend = 0.02), and any allergic symptoms (P for trend = 0.004) were significantly lower with higher amounts of fruit intake (Table 3). In addition, compared with children in the low fruit intake group, those in the medium (OR: 0.40; 95%CI: 0.16–0.99) and high intake groups (OR: 0.44; 95%CI: 0.002–0.85) showed a significantly lower prevalence of asthma symptoms, and those in the high intake group showed a significantly lower prevalence of rhinitis symptoms (OR: 0.37; 95%CI: 0.16–0.84) and any allergic symptoms (OR: 0.31; 95%CI: 0.14–0.68) (Table 3). No significant relationship was observed for the prevalence of eczema, or between these allergic symptoms and vegetable, fish, or bean intake (Table 3).

Amount of food intake and new onset allergic symptoms

Among the children with no rhinitis symptoms at the start of the study (n=378), the prevalence of those developing new onset rhinitis symptoms during the study period was significantly lower with higher amounts of fruit intake (P for trend =

0.04) (Table 4). The same significance was observed for new onset any allergic symptoms (P for trend = 0.01) (Table 4). However, no such significance was observed for asthma symptoms (n=460) or eczema symptoms (n=425). In addition, no significance was observed between these new onset allergic symptoms and vegetable, fish, or bean intake. One exception was the relationship between new onset asthma symptoms and fish intake, in which the prevalence of new onset asthma symptoms during the study period was significantly lower with higher amounts of fish intake (P for trend = 0.02) (Table 3). Also, compared with those in the low fish intake group, those in the medium fish intake group showed a significantly lower prevalence of new onset asthma symptoms (OR: 0.22; 95%CI: 0.06–0.89) (Table 4).

Amount of food intake and recovered allergic symptoms

Among those with asthma symptoms at the start of the study (n=60), the prevalence of those with recovery of symptoms during the study period was significantly higher with higher amounts of fruit intake (P for trend = 0.02) (Table 5). No significant difference was observed in the recovery of rhinitis (n=142), eczema (n=95) or any allergic symptoms (n=219), respectively (Table 5).

Amount of fruit intake and sensitization to inhalant allergens at 10 years of age

In 2014, blood samples were obtained from 491 children. The distribution of children who were positive to either house dust mites, Japanese cedar, orchard

grass, or any of these allergens at 10 years of age was not significantly different, regardless of the amount of fruit intake (Table 6). However, the distribution of those who were positive for specific IgE to ragweed was significantly lower with higher amounts of fruit intake (P for trend = 0.046) (Table 6). Also, compared with those in the low fruit intake group, those in the medium fruit intake group showed a significantly lower positive rate for ragweed (OR: 0.48; 95%CI: 0.25–0.93) (Table 6).

Discussion

We found a significant negative association between fruit intake and the onset of respiratory allergic symptoms based on prospective data from schoolchildren. This finding is in line with the recent results of an overview of systemic reviews that showed evidence of a negative association between asthma or wheeze and dietary intake of vitamins C, E, and D, as well as intake of fruits and adherence to a Mediterranean diet (25). Our results also show that the sensitization rate of ragweed antigen was significantly lower with higher amounts of fruit intake. No similar trend was observed for any of the other inhalant allergens tested. The sensitization rates of other allergens were higher than that of ragweed (average sensitization rates of other allergens: 36.0–52.5%; average sensitization rate of ragweed: 17.5%). This could have been because the sensitization of other allergens was too high to observe any specific effect of fruit intake. Other foods that supposedly have allergy suppressive effects did not show any such effect in

the present study, except for new onset asthma symptoms and fish intake, indicating that the effect is specific to fruit intake.

Rosenlund et al. (26) observed a similar reverse association between fruit intake and the prevalence of rhinitis in Swedish children, but the significance disappeared after excluding those with a history of food-induced allergic symptoms. They argued that disease-related modifications of consumption patterns contributed to this association. However, according to multivariate analysis, in the present study, when experience of food avoidance was included as a confounding factor, the significant suppressive effect of fruit intake on allergic symptoms remained, indicating that there was no evidence of such an association in our study.

Although the immunomodulatory mechanisms by which fruit intake suppress allergic symptoms remain unclear, antioxidants in fruits have been considered a possible cause; this warrants further investigation (4, 5). In addition, dietary polyphenols found in fruits have been shown to affect multiple biologic pathways and immune cell functions in the allergic immune response (27). The primary mechanisms underlying the inhibitory effects on allergy development by polyphenols appear to be suppression of T-helper 2 cells and activation of T-regulatory cells (28).

In the present study, fruit intake showed a markedly negative association with asthma and rhinitis symptoms, but no such effects were seen for eczema symptoms, suggesting that fruit intake is only effective for helping to prevent respiratory allergic symptoms. The epidemiological association between asthma

and rhinitis is well known, and pathophysiological studies have suggested that these two conditions share various similarities and differences (29). In accordance with this observation, the sensitization rate to ragweed was significantly lower with higher amounts of fruit intake. Meanwhile, except for asthma symptoms, fruit intake did not improve the existing allergic symptoms. In this sense, adequate consumption of fruit since early childhood might be a critical factor in obtaining a sufficient allergy suppressive association.

This study did have several limitations. First, we did not actually observe the symptoms or the diet contents because these data were obtained from self-administered questionnaires, even though both the ISAAC and BDHQ questionnaires are well validated and widely used. Second, we did not analyze data regarding the kinds of fruit consumed by the participants; this should be evaluated in a future study. Third, as this was a questionnaire survey, there is a possibility of recall bias. Fourth, family socioeconomic status might be a confounding factor in regard to fruit intake. Finally, the season in which the BDHQ questionnaires were delivered may have affected the fruit intake based on obtainability.

The average of the lowest amount of fruit consumed in the fourth quartile in each year was 85 g. One mandarin orange, one banana, and one-third of an apple correspond to approximately 100 g of fruit; therefore, the continued consumption of these amounts, for example, might be appropriate for children to promote an allergy-suppressive association. Obviously, fruit intake is not recommended for those with fruit allergies, although only two children in our study eliminated fruit

from their diets because of a suspected fruit allergy. We performed the same analysis after excluding these two participants and found the same results (data not shown). It would be interesting to examine whether fruit intake since early childhood prevents the development of fruit allergies, as reported for peanut allergies in a previous study (30), or of sensitization to pollen allergens, which have cross-reactivity to fruit.

In conclusion, fruit intake significantly suppressed the onset of respiratory allergic symptoms and sensitization to ragweed in schoolchildren. These results suggest that encouraging children to consume high amounts of fruit can help prevent respiratory allergic symptoms.

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Table 1. Background characteristics of the schoolchildren (enrolled vs. unenrolled)

	Enrolled (n=520)	Unenrolled (n=147)	P value
Male sex	245/518 (47.3%)	76/146 (52.1%)	0.31
Season of birth (October to March)	267/518 (51.5%)	72/147 (49.0%)	0.58
Low birth weight (<2,500g)	41/518 (7.9%)	18/145 (12.4%)	0.09
First born	270/510 (52.9%)	68/141 (48.2%)	0.32
Allergy in parents	328/519 (63.2%)	78/147 (53.1%)	0.03
Complete breastfeeding for ≥ 6 months	165/512 (32.2%)	42/139 (30.2%)	0.65
Experience of food avoidance	42/520 (8.1%)	5/122 (4.1%)	0.13
Asthma symptom at 7 years of age	60/520 (11.5%)	9/122 (7.4%)	0.18
Eczema symptom at 7 years of age	95/520 (18.3%)	18/122 (14.8%)	0.36
Rhinitis symptom at 7 years of age	142/520 (27.3%)	24/122 (19.7%)	0.08

Table 2. Amount of food intake according to age

	Age (yrs)			
	7	8	9	10
Fruit	68.0± 45.7	63.6±42.5	60.2±37.1	58.9±40.0
Vegetables	78.0± 32.7	75.0±30.6	76.0±31.0	76.3±32.5
Fish	47.9±22.3	47.2±22.2	48.5±24.3	46.6±21.8
Beans	40.7±23.9	39.7±23.5	38.6±20.9	40.8±23.3

Data (g/day) were shown as average ± SD

Table 3. Food intake and allergic symptoms at 10 years of age (n=520)

Symptom	Food	Intake	Prevalence of symptom (%)	Multivariate OR* (95%CI)	P for trend
Asthma	Fruit	Low	8/63 (12.7)	Ref.	0.003
		Medium	27/395 (6.8)	0.40 (0.16–0.99)	
		High	0/62 (0.0)	0.44 (0.002–0.85)	
	Vegetables	Low	3/67 (4.5)	Ref.	0.50
		Medium	30/397 (7.6)	1.22 (0.33–4.47)	
		High	2/56 (3.6)	0.51 (0.08–3.29)	
	Fish	Low	7/51 (13.7)	Ref.	0.08
		Medium	27/423 (6.4)	0.59 (0.22–1.59)	
		High	1/46 (2.2)	0.16 (0.02–1.46)	
Eczema	Beans	Low	2/51 (3.9)	Ref.	0.99
		Medium	29/410 (7.1)	1.17 (0.26–5.26)	
		High	4/59 (6.8)	1.06 (0.18–6.32)	
	Fruit	Low	9/63 (14.3)	Ref.	0.37
		Medium	72/395 (18.2)	1.23 (0.54–2.80)	
		High	6/62 (9.7)	0.60 (0.19–1.95)	
	Vegetable	Low	10/67 (14.9)	Ref.	0.98

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		Medium	67/397 (16.9)	1.05 (0.48–2.29)	
		High	10/56 (17.9)	1.02 (0.37–2.81)	
Fish	Low		9/51 (17.6)	Ref.	0.50
		Medium	72/423 (17.0)	1.12 (0.49–2.60)	
		High	6/46 (13.0)	0.64 (0.19–2.13)	
Beans	Low		7/51 (13.7)	Ref.	0.82
		Medium	69/410 (16.8)	1.35 (0.53–3.42)	
		High	11/59 (18.6)	1.22 (0.40–3.71)	
Rhinitis	Fruit	Low	24/63 (38.1)	Ref.	0.02
		Medium	142/395 (35.9)	0.78 (0.44–1.40)	
		High	13/62 (21.0)	0.37 (0.16–0.84)	
Vegetables	Low		17/67 (25.4)	Ref.	0.35
		Medium	141/397 (35.5)	1.49 (0.80–2.75)	
		High	21/56 (37.5)	1.47 (0.66–3.26)	
Fish	Low		21/51 (41.2)	Ref.	0.08
		Medium	146/423 (34.5)	0.82 (0.43–1.53)	
		High	12/46 (26.1)	0.45 (0.18–1.09)	

	Beans	Low	13/51 (25.5)	Ref.	0.99
		Medium	147/410 (35.9)	1.47 (0.74–2.93)	
		High	19/59 (32.2)	1.08 (0.46–2.56)	
Any	Fruit	Low	30/63 (47.6)	Ref.	0.004
		Medium	190/395 (48.1)	0.84 (0.47–1.49)	
		High	16/62 (25.8)	0.31 (0.14–0.68)	
	Vegetables	Low	25/67 (37.3)	Ref.	0.58
		Medium	184/397 (46.3)	1.27 (0.72–2.23)	
		High	27/56 (48.2)	1.23 (0.58–2.61)	
	Fish	Low	25/51 (49.0)	Ref.	0.14
		Medium	194/423 (45.9)	0.93 (0.50–1.74)	
		High	17/46 (37.0)	0.52 (0.22–1.21)	
	Beans	Low	19/51 (37.3)	Ref.	0.96
		Medium	192/410 (46.8)	1.46 (0.77–2.77)	
		High	25/59 (42.4)	0.99 (0.44–2.21)	

* Sex, season of birth, low birth weight, birth order, parent's allergies, breastfeeding, and experience of food avoidance were included as confounding factors.

OR, odds ratio; *CI*, confidence interval.

Table 4. Food intake and new onset allergic symptoms in schoolchildren

Symptom	Food	Intake	Prevalence of new onset symptom (%)	Multivariate OR* (95%CI)	P for trend
Asthma (n=460)	Fruit	Low	3/55 (5.5)	Ref.	0.13
		Medium	7/344 (2.0)	0.37 (0.08–1.66)	
		High	0/61 (0.0)	0.20 (0.01–4.30)	
	Vegetables	Low	1/57 (1.8)	Ref.	0.77
		Medium	8/350 (2.3)	0.76 (0.12–4.72)	
		High	1/53 (1.9)	0.67 (0.06–7.56)	
	Fish	Low	4/44 (9.1)	Ref.	0.02
		Medium	6/375 (1.6)	0.22 (0.06–0.89)	
		High	0/41 (0.0)	0.11 (0.005–2.47)	
Eczema (n=425)	Beans	Low	0/44 (0.0)	Ref.	0.84
		Medium	9/361 (2.5)	2.81 (0.15–53.57)	
		High	1/55 (1.8)	1.83 (0.07–48.84)	
	Fruit	Low	4/53 (7.5)	Ref.	0.93
		Medium	28/319 (8.8)	1.55 (0.44–5.50)	
		High	3/53 (5.7)	1.06 (0.19–5.78)	
	Vegetables	Low	4/56 (7.1)	Ref.	0.59
		Medium	29/324 (9.0)	1.32 (0.42–4.18)	
		High	2/45 (4.4)	0.54 (0.09–3.26)	
Rhinitis (n=378)	Fish	Low	6/45 (13.3)	Ref.	0.15
		Medium	27/342 (7.9)	0.57 (0.20–1.63)	
		High	2/38 (5.3)	0.28 (0.05–1.73)	
	Beans	Low	3/45 (6.7)	Ref.	0.20
		Medium	26/332 (7.8)	2.04 (0.45–9.24)	
		High	6/48 (12.5)	2.95 (0.54–15.99)	
	Fruit	Low	13/47 (27.7)	Ref.	0.04
		Medium	65/283 (23.0)	0.68 (0.32–1.44)	
		High	6/48 (12.5)	0.32 (0.10–0.96)	
	Vegetables	Low	5/52 (9.6)	Ref.	0.14
		Medium	70/289 (24.2)	2.82 (1.05–7.58)	
		High	9/37 (24.3)	2.50 (0.75–8.37)	
	Fish	Low	10/37 (27.0)	Ref.	0.16
		Medium	69/307 (22.5)	0.82 (0.36–1.89)	
		High	5/34 (14.7)	0.40 (0.12–1.41)	

	Beans	Low	6/38 (15.8)	Ref.	0.67
		Medium	67/295 (22.7)	1.33 (0.51–3.45)	
		High	11/45 (24.4)	1.33 (0.43–4.13)	
Any (n=301)	Fruit	Low	12/36 (33.3)	Ref.	0.01
		Medium	63/223 (28.3)	0.63 (0.28–1.44)	
		High	6/42 (14.3)	0.22 (0.07–1.44)	
	Vegetables	Low	6/39 (15.4)	Ref.	0.28
		Medium	64/227 (28.2)	2.10 (0.81–5.47)	
		High	11/35 (31.4)	2.00 (0.63–6.34)	
	Fish	Low	9/30 (30.0)	Ref.	0.35
		Medium	66/244 (27.0)	0.92 (0.38–2.25)	
		High	6/27 (22.2)	0.54 (0.15–1.91)	
	Beans	Low	7/32 (21.9)	Ref.	0.67
		Medium	62/229 (27.1)	1.51 (0.57–4.01)	
		High	12/40 (30.0)	1.39 (0.44–4.41)	

* Sex, season of birth, low birth weight, birth order, parent's allergies, breastfeeding, and experience of food avoidance were included as confounding factors.

Table 5. Fruit intake and recovered allergic symptoms in schoolchildren

Symptom	Fruit intake	Prevalence of recovered symptom (%)	Multivariate OR* (95%CI)	P for trend
Asthma (n=60)	Low	3/8 (37.5)	Ref.	0.02
	Medium	31/51 (60.8)	5.57 (0.96–32.17)	
	High	1/1 (100.0)	16.5 (0.38–718.50)	
Eczema (n=95)	Low	5/10 (50.0)	Ref.	0.21
	Medium	32/76 (42.1)	1.18 (0.26–5.28)	
	High	6/9 (66.7)	4.09 (0.49–34.09)	
Rhinitis (n=142)	Low	5/16 (31.3)	Ref.	0.18
	Medium	35/112 (31.3)	1.10 (0.34–3.60)	
	High	7/14 (50.0)	3.16 (0.63–15.72)	
Any (n=219)	Low	12/27 (44.4)	Ref.	0.17
	Medium	84/172 (48.8)	1.37 (0.57–3.29)	
	High	12/20 (60.0)	2.46 (0.69–8.71)	

* Sex, season of birth, low birth weight, birth order, parent's allergies, breastfeeding, and experience of food avoidance were included as confounding factors.

Allergen	Fruit intake	Positive rate (%)	Multivariate OR* (95%CI)	P for trend
House dust mites	Low	32/57 (56.1)	Ref.	0.24
	Medium	200/375 (53.3)	0.79 (0.44–1.42)	
	High	26/59 (44.1)	0.63 (0.30–1.35)	
Japanese cedar	Low	27/57 (47.4)	Ref.	0.82
	Medium	200/375 (53.3)	1.20 (0.67–2.14)	
	High	27/59 (45.8)	0.92 (0.43–1.96)	
Orchard grass	Low	22/57 (38.6)	Ref.	0.17
	Medium	139/375 (37.1)	0.83 (0.46–1.50)	
	High	16/59 (27.1)	0.57 (0.25–1.27)	
Ragweed	Low	15/57 (26.3)	Ref.	0.046
	Medium	63 /375(16.8)	0.48 (0.25–0.93)	
	High	8/59 (13.6)	0.40 (0.15–1.05)	
Any allergen	Low	40/57 (70.2)	Ref.	0.13
	Medium	272/375 (72.5)	0.97 (0.51–1.83)	
	High	35/59 (59.3)	0.55 (0.25–1.24)	

Table 6. Fruit intake and sensitization to inhalant allergens at 10 years of age

* Sex, season of birth, low birth weight, birth order, parent's allergies, breastfeeding, and experience of food avoidance were included as confounding factors

Sensitization was defined as the level of specific immunoglobulin E ≥ 0.7 UA/mL.

Table S1

Amount of fruit intake and allergic symptoms at 10 years of age

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.006
	medium	0.52(0.23-1.13)	
	high	0.17(0.05-0.66)	
eczema	low	Ref	0.23
	medium	1.03(0.57-1.88)	
	high	0.63(0.30-1.33)	
rhinitis	low	Ref	0.38
	medium	0.96(0.60-1.53)	
	high	0.79(0.46-1.35)	
any symptom	low	Ref	0.07
	medium	0.88(0.56-1.38)	
	high	0.61(0.36-1.03)	

Amount of fruit intake and new-onset allergic symptoms

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.11
	medium	0.61(0.16-2.40)	
	high	0.12(0.006-2.38)	
eczema	low	Ref	0.40
	medium	0.71(0.30-1.69)	
	high	0.65(0.23-1.85)	
rhinitis	low	Ref	0.19
	medium	0.59(0.32-1.08)	
	high	0.64(0.32-1.28)	
any symptom	low	Ref	0.11
	medium	0.65(0.34-1.26)	

high 0.54(0.26-1.16)

Amount of fruit intake and recovered allergic symptoms

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.09
	medium	1.79(0.43-7.55)	
	high	5.38(0.80-35.94)	
eczema	low	Ref	0.12
	medium	1.03(0.32-3.32)	
	high	2.85(0.70-11.60)	
rhinitis	low	Ref	0.53
	medium	0.54(0.21-1.41)	
	high	1.29(0.44-3.10)	
any symptom	low	Ref	0.06
	medium	0.77(0.38-1.57)	
	high	2.26(0.97-5.28)	

Amount of fruit intake and sensitization to inhalant allergens

allergen	amount	multiple OR(95%CI)	p for trend
house dust mite	low	Ref	0.69
	medium	0.92(0.59-1.45)	
	high	0.90(0.53-1.51)	
Japanese cedar	low	Ref	0.69
	medium	0.92(0.59-1.45)	
	high	0.90(0.53-1.51)	
orchard grass	low	Ref	0.03
	medium	0.63(0.39-0.99)	
	high	0.55(0.32-0.94)	
ragweed	low	Ref	0.02

	medium	0.39(0.22-0.97)	
	high	0.45(0.23-0.87)	
any allergen	low	Ref	0.37
	medium	0.78(0.47-1.30)	
	high	0.76(0.43-1.36)	

Table S2

Amount of fruit intake and allergic symptoms at 10 years of age

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.08
	medium	0.28(0.06-1.28)	
	high	0.19(0.008-4.18)	
eczema	low	Ref	0.66
	medium	1.23(0.34-4.43)	
	high	0.61(0.09-4.15)	
rhinitis	low	Ref	0.02
	medium	0.54(0.25-1.16)	
	high	0.27(0.09-0.84)	
any symptom	low	Ref	0.02
	medium	0.46(0.19-1.13)	
	high	0.17(0.04-0.62)	

Amount of fruit intake and new-onset allergic symptoms

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.10
	medium	0.33(0.07-1.45)	
	high	0.21(0.01-4.51)	
eczema	low	Ref	0.54
	medium	1.18(0.33-4.14)	
	high	0.54(0.08-3.50)	
rhinitis	low	Ref	0.04
	medium	0.56(0.27-1.14)	
	high	0.33(0.11-0.99)	
any symptom	low	Ref	0.04
	medium	0.65(0.34-1.27)	

high 0.35(0.13-0.94)

Amount of fruit intake and recovered allergic symptoms

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.02
	medium	8.87(1.15-68.25)	
	high	24.07(1.05-550.21)	
eczema	low	Ref	0.40
	medium	2.26(0.43-11.98)	
	high	2.59(0.30-22.29)	
rhinitis	low	Ref	0.94
	medium	0.91(0.26-3.24)	
	high	1.14(0.17-7.84)	
any symptom	low	Ref	0.25
	medium	1.58(0.62-34.98)	
	high	2.14(0.59-7.81)	

Amount of fruit intake and sensitization to inhalant allergens

allergen	amount	multiple OR(95%CI)	p for trend
house dust mite	low	Ref	0.07
	medium	0.76(0.40-1.43)	
	high	0.47(0.20-1.08)	
Japanese cedar	low	Ref	0.60
	medium	1.09(0.58-2.04)	
	high	0.82(0.36-1.86)	
orchard grass	low	Ref	0.12
	medium	0.74(0.39-1.40)	
	high	0.50(0.21-1.20)	
ragweed	low	Ref	0.13

	medium	0.50(0.24-1.03)	
	high	0.46(0.17-1.28)	
any allergen	low	Ref	0.20
	medium	0.92(0.46-1.84)	
	high	0.57(0.24-1.39)	

Table S3

Amount of fruit intake and allergic symptoms at 10 years of age

(obesity was added as a confounding factor)

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.003
	medium	0.39(0.16-0.97)	
	high	0.05(0.002-0.96)	
eczema	low	Ref	0.37
	medium	1.23(0.54-2.81)	
	high	0.58(0.18-1.87)	
rhinitis	low	Ref	0.02
	medium	0.76(0.43-1.37)	
	high	0.36(0.15-0.82)	
any symptom	low	Ref	0.004
	medium	0.84(0.47-1.49)	
	high	0.31(0.14-0.68)	

Amount of fruit intake and new-onset allergic symptoms

(obesity was added as one of the confounding factors)

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.097
	medium	0.35(0.08-1.57)	
	high	0.15(0.006-3.45)	
eczema	low	Ref	0.85
	medium	1.23(0.38-4.05)	
	high	0.86(0.17-4.24)	
rhinitis	low	Ref	0.03

	medium	0.64(0.30-1.35)	
	high	0.30(0.10-0.92)	
any symptom	low	Ref	0.009
	medium	0.60(0.26-1.39)	
	high	0.21(0.06-0.68)	

Amount of fruit intake and recovered allergic symptoms
(obesity was added as a confounding factor)

symptom	amount	multiple OR(95%CI)	p for trend
asthma	low	Ref	0.04
	medium	5.54(0.91-33.81)	
	high	15.21(0.34-674.79)	
eczema	low	Ref	0.22
	medium	1.19(0.26-4.41)	
	high	4.24(0.49-36.46)	
rhinitis	low	Ref	0.19
	medium	1.13(0.34-3.72)	
	high	3.04(0.61-15.28)	
any symptom	low	Ref	0.19
	medium	1.37(0.57-3.29)	
	high	2.45(0.69-8.72)	

Amount of fruit intake and sensitization to inhalant allergens
(obesity was added as a confounding factor)

allergen	amount	multiple OR(95%CI)	p for trend
house dust mite	low	Ref	0.23
	medium	0.79(0.44-1.42)	
	high	0.63(0.29-1.35)	

Japanese cedar	low	Ref	0.71
	medium	1.14(0.64-2.05)	
	high	0.88(0.41-1.87)	
orchard grass	low	Ref	0.15
	medium	0.81(0.40-1.46)	
	high	0.55(0.25-1.23)	
ragweed	low	Ref	0.05
	medium	0.49(0.25-0.95)	
	high	0.40(0.15-1.07)	
any allergen	low	Ref	0.11
	medium	0.93(0.49-1.77)	
	high	0.53(0.24-1.20)	

Data S1.

BDHQ-10y questionnaire regarding fruit intake

a) How often did you eat the following fruits in the past month (other than during school lunch)?

#mandarin orange, grapefruit, and other citrus fruits

#Japanese persimmon, strawberry, and kiwi

#other fruits

Choices: twice or more every day, once every day, 4 to 6 times per week, 2 to 3 times per week, once a week, less than once a week, never

b) How much of one person's portion of fruit do you eat during school lunch?

Choices: small portion, about half, more than half, all, I sometimes have a second helping, I usually have a second helping

c) During the past year, how often did you eat the following fruits in the season during which you ate most often?

#mandarin oranges

#Japanese persimmons

#strawberries

Choices: twice or more every day, once every day, 4 to 6 times per week, 2 to 3 times per week, once a week, less than once a week, never

Supplementary Data S2.

Asthma symptoms were estimated on the basis of positive answers to one question ("Has your child experienced wheezing or whistling in the chest in the past 12 months?"), eczema symptoms were estimated on the basis of positive answers to two questions ("Has your child experienced an itchy rash at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows; behind the knees; in front

of the ankles; under the buttocks; or around the neck, ears, or eyes.”). Rhinitis symptoms were estimated on the basis of positive answers to the questions “In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?” and “In the past 12 months, how much did this nasal problem interfere with your child’s daily activities?” for any answer except for “Not at all” (i.e., “A little”, “A moderate amount”, or “A large amount”).