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Relationship between growth and food avoidance with food allergy at age 3 years: The Japan Environment and Children's Study (JECS)

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ABSTRACT

Background: Basic management for food allergy (FA) is eliminating causative food from the diet, which can impact normal growth. This study examined the association between food avoidance and growth failure among children with FA aged 0–3 years using the Japan Environment and Children's Study (JECS) data.

Methods: Data on height, weight, and FA history registered were collected using self-administered questionnaires at age 1, 1.5, 2, and 3 years. A general linear model was used to examine whether dietary restriction affected body size. Height, weight, and body mass index (BMI) were adjusted for age in months using standard deviation (SD) scores for each age group by month of measurement. Presence of FA or dietary restriction was used as a binary variable.

Results: Of the 38 477 participants included in this analysis, 4070 with FAs had significantly lower SD scores for height and weight at age 3 years. With milk avoidance, significantly lower SD scores for height (male: $\beta = -0.097$ [95%CI: 0.175, −0.019], female: $\beta = -0.103$ [95%CI: 0.204, −0.002]), a significantly lower SD score for weight (male: $\beta = -0.115$[95%CI: 0.187, −0.043], female $\beta = -0.114$[95%CI: 0.203, −0.026]) were observed. Soy avoidance in males marked a lower SD score for height ($\beta = -0.307$ [95%CI: 0.474, −0.140]). Continued food avoidance until age 3 resulted in significantly lower SD score for height and weight regardless of gender.

Conclusion: Growth impairment was observed with food avoidance at age 3 years. Growth impairment were more obvious in males than in females. With regards food items, the impact of milk and soy was more significant.

Keywords: Food allergy, Food avoidance, Growth, Infancy, Gender differences

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INTRODUCTION

In recent years, the prevalence of food allergies (FAs) has increased worldwide.[1] FA can occur during early stages of life. In a previous cohort study by the Japan Environment and Children's Study (JECS), the prevalence of caregiver-reported immediate FA was 7.6%, 6.7%, and 4.9% at ages 1, 2, and 3 years, respectively.[2] Percentage of foods that cause FA depends on food culture, and therefore varies according to area of residence. In Japan, the top-ranked foods which caused immediate food allergy by age are: eggs, milk, wheat in 0-year-olds; eggs, milk, nuts, fish eggs, peanuts, and wheat in 1–2 year-olds; and nuts, milk, egg, peanuts, fish eggs, and wheat in 3–6-year-olds.[3] FA develops in infancy, when nutrition is required for growth and development. Furthermore, children may have multiple FAs, which requires avoidance of several food items simultaneously. The basic management for FA is avoidance of the causative food.[1] Importantly, prolonged avoidance of a food item can lead to failure to thrive. However, there are only a few population-based studies on the extent to which growth failure can occur, depending on the food avoided, number of food items avoided, and length of avoidance. Some studies demonstrated that failure to thrive is due to the avoidance of milk products, which are one of the most common foods causing FAs in infancy.[4–6] However, some studies reported no significant differences based on the avoided food.[4] Therefore, the relationship between food avoidance and failure to thrive remains controversial.

JECS is a large-scale, nationwide, multicenter, prospective birth cohort study that began in January 2011. It was implemented as a national project funded by the Ministry of Environment, Japan. Its main objective is to elucidate the environmental factors that affect children's health and development. This study aimed to evaluate the growth and risk factors associated with failure to thrive in children with FA (complications and food avoidance) at age 3 years using the JECS data.

METHODS

Study design and participants

JECS has 15 Regional Centers in Japan.[7] Pregnant women, in their first trimester, who visited a maternity hospital in the Regional Centers and centers related to the JECS, or the reception counter of a municipality office, to get a Maternal and Child Health Handbook provided by local public organizations were recruited in this cohort study between January 2011 and March 2014. After registration, 104 062 fetuses from registered pregnant women were included in this study. The data for the children were collected at birth, 1 year, 1.5 years, 2 years, and 3 years using self-administered questionnaires. The data for this study were extracted from a dataset released in October 2019 (dataset jecs-ta-20190930).

Questionnaires: The questionnaire survey was conducted every 6 months from 0 to 3 years.

Questions for FA were as follows: "Diagnosed with FA by doctor." 0 = no, 1 = yes.

"Allergic symptoms after eating specific foods within 3 h" 0 = no, 1 = yes. Detailed allergic symptoms were follows; hives, itchiness, swelling on the face or lips. Sneezing, running nose, itchiness or uncomfortable feeling in the mouth. Coughing, wheezing. Vomiting, diarrhea, stomachache. Decrease in blood pressure, convulsion, loss of consciousness.

Questions regarding consumption status and food avoidance were as follows: "Consumption status and reaction to specific foods." 1 = no avoidance (eating normally), 2 = has never eaten, 3 = partial avoidance, 4 = has eaten before, however, now complete avoidance. Avoided food items: Eggs and/or egg ingredients 0 = no, 1 = yes; milk (including milk powder, cheese) 0 = no, 1 = yes; wheat 0 = no, 1 = yes; soybean 0 = no, 1 = yes; fish 0 = no, 1 = yes; rice 0 = no, 1 = yes; fruit 0 = no, 1 = yes.

Definitions

Definition of FA and non-FA: Defined as FA when answered "Yes" to both of the following questions:1) "Diagnosed with FA by doctor" at the age of 1 or 1.5 or 2 years; and 2) "Experienced any adverse symptoms within 3 h after drinking and/or eating specific foods" at the age of 1 or 1.5 or 2 years. Defined as non-FA when the previous 2 conditions were not satisfied. Participants who did

not meet the definitions of FA and non-FA were excluded.

Definition of food avoidance: questionnaires at the age of 1.5 and 2 years were used. If answered "has never eaten," "partial avoidance," "has eaten before, however, now complete avoidance" for even one of the 7 foods (eggs, milk, wheat, soy, fish, rice, or fruit), it was defined as food avoidance.

Duration of food avoidance: questionnaires 1.5-, 2-, and 3-years and was divided into 5 categories: 1) no dietary restriction; 2) answered "Yes" in questionnaires asked at 1.5 years; 3) answered "Yes" in questionnaires asked at 1.5 and 2 years; 4) answered "Yes" in questionnaires administered at 1.5, 2, and 3 years; and 5) and the others. "The others" were defined when answered "Yes" only in the questionnaires as follows: a) 1.5 years and 3 years, or b) at 2 years, or c) at 2 years and 3 years.

Records of height and weight: Data from medical record transcripts at birth and self-administered questionnaires at 3 years of age were used. Except for the records at birth, recent height and weight were measured at the co-operating healthcare providers, clinics, nursery facilities, or homes. At the 3 years questionnaires, we excluded measurements outside the rage of 34–38 months to eliminate the difference in body size due to the time of measurement. The SD scores were calculated using the Lambda-mu-sigma (LMS) method, referring to the LMS values of height and weight in Japanese children.[8] As well, body mass index-SD (BMI-SD) was calculated with the following references.[9]

Definition of complications: questionnaires for bronchial asthma (BA) and atopic dermatitis (AD) were as follows.[10–12] "Diagnosed by a doctor with any of the following diseases?": Bronchial asthma、1 = yes, 2 = no; Atopic dermatitis、1 = yes, 2 = no; "Diagnosed by a doctor" and answered "Yes" to both of the following two questions either at age 1, 1.5, 2, or 3 years was considered to have a positive history.

Two questions regarding BA were: 1) Has your child ever had wheezing or whistling in the chest at any time in the past? 2) Has your child had wheezing or whistling in the chest in the past 12 months?

Two questions regarding AD were:1) Has your child ever had an itchy recurring rash for at least 6 months? (More than 2 months in the questionnaire administered at 1 year); 2) Has your child ever had an itchy rash at any time in the past 12 months?

Definition of mother's history of allergic disease: questionnaire filled at the time of JECS study registration. "Have you ever been diagnosed of the following disease by a doctor?" Bronchial asthma, 1 = yes, 2 = no; Atopic dermatitis, 1 = yes, 2 = no; Food allergy, 1 = yes, 2 = no. Answered "Yes" to either of the diseases was considered as a positive history for allergic disease for mothers.

Definition of mother's height and weight: Information was collected from either of the following sources: 1) doctor's questionnaire when expecting delivery date was determined, 2) at the registration for the JECS study, or 3) maternal health examination transcription form.

Definition of annual household income: second/third trimester questionnaire was used. "How much is your annual household income?" The answer section is for every 2 million Japanese yen (JPY) over 2 to 20 million yen. In analyzing the data, we categorized the study population into 3 categories of approximately same size: 1) less than 4 million JPY, 2) 4–6 million JPY, and 3) $\geq$6 million JPY.

Statistical analysis

A generalized linear model was used, with the SD score of height or weight as the dependent variable, presence of food allergy and each of the eliminated foods (egg, milk, wheat, soy, fish, rice, and fruit) as independent variables. Maternal height and weight, maternal history of allergic disease, height and weight at birth of the child, history of atopic dermatitis and asthma, and household income were used as covariates, and were analyzed separately for male and female.

In order to further evaluate the impact of the removal of individual food items, each of the above eliminated food items were analyzed as an independent variable.

A generalized linear model was used to assess whether body size affected by food avoidance was influenced by allergic complications. The interaction between food avoidance of either of the 7

items and allergic complications was estimated by adjusting for the covariates.

We stratified the analysis by household income and estimated the difference in the SD scores with or without food avoidance by adjusting for covariates using a generalized linear model.

SAS ver 9.4 (SAS Institute Inc.) was used for the statistical analysis.

RESULTS

JECS collected data on 104 062 fetuses and 100 303 live births. Overall, 1891 multiple births and 18 unknown genders were excluded. Further, 10,255 records with low birth weight (less than 2500 g), preterm births (< 37 weeks), and post-term births (≥42 weeks) were excluded. Moreover, 13 712 cases with physical abnormalities, such as congenital heart disease and chromosomal abnormalities, were also excluded, since they may affect growth. Furthermore, 19 037 records were excluded due to unsuccessful follow-ups or insufficient answers regarding food avoidance, height and weight, and 8756 records measured outside the range of 34–38 months of age were excluded. Additionally, 2185 records with unknown covariates and 5972 records that did not meet the definitions of FA or non-FA were excluded. 36 118 children were included in this study (Fig. 1) and were divided into 2 groups. FA group: n = 4070, Non-FA group: n = 34 407. Records indicating avoidance of food items for reasons other than FA (n = 2359) were excluded. And so the final number of the non-FA group were 32048 children.

The baseline clinical characteristics of the 2 groups are summarized in Table 1. The number of males in the FA group was greater than that of females. (male: female = 57.4%: 42.6%). Among the 2 groups, complications, such as BA and AD, were frequently observed in the FA group (Group 1). In Group 1, AD was found in 28.3% of the children. The mean birth weight, birth height, showed little difference among the 2 groups.

Our results revealed that children with FA exhibited significantly lower SD scores for height and weight regardless of gender (Table 1).

Eggs were the most frequently avoided food by children with FA, followed by milk and wheat. Children who had avoided milk had significantly lower SD scores for both height and weight. Males who had avoided soy presented significantly lower SD scores for height. Males who had avoided fruits and females who avoided rice showed significantly lower SD in weight. No foods differed significantly in BMI-SD. (Table 2)

Children with FA may have to avoid multiple food items. The avoided food items could be combined into numerous combinations; further, statistical analysis of these numerous combinations was impossible. Therefore, we calculated the variation in height, weight and BMI when only 1 food item was avoided. The results were much the same. Even in the presence of multiple food avoidances, the effect on the amount of change in each item was considered to be small (Table 3).

The longer the period of food avoidance, the greater the effect was, regardless of gender. For food avoidance continued until age 3 years, both genders exhibited a decreased SD score for height, weight and BMI (Table 4).

In view of the history of allergic disease, children with AD had significantly lower SD scores for height and weight at age 3 years. A significant interaction was found between AD and FA in female BMI-SD score (Table 5).

When the household income was <4 million yen, males had a significantly lower SD score for height and weight at age 3 years (Table 6).

DISCUSSION

This report is the largest of its kind to examine the effects of food avoidance on growth in early childhood. In 1998, Isolauri et al first reported an association between FAs and impaired growth in children with milk elimination.[13] Since then, similar studies have been conducted sporadically.[5,6,14] We analyzed how avoiding food items can affect the growth of 0–3-year-old children with FAs.

Another epidemiological survey, conducted by doctors specializing in allergies in Japan enrolled participants who had any reaction within 60 min of ingesting food and visited a medical facility, reported that, by gender, the male-to-female ratio was 1.36, but differed by age group. Males were more prevalent in the 0 and 7–17 age groups,

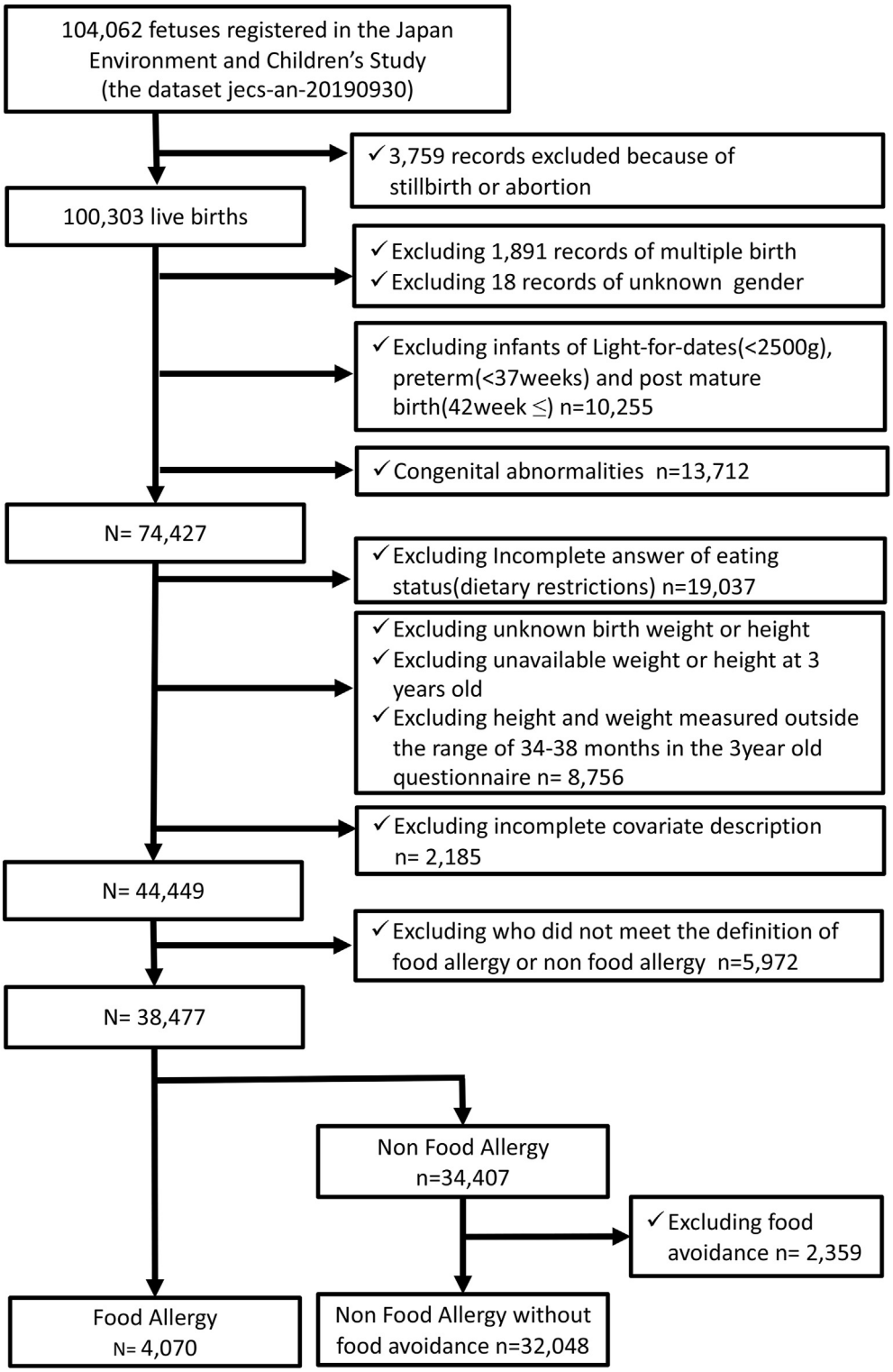

Fig. 1 Flow chart of the study participants.

	Food Allergy (n = 4070)		Non Food Allergy (n = 32,048)	
	n	(%)	n	(%)
Gender				
Male	2336	57.4	15 977	49.9
Female	1734	42.6	16 071	50.1
Allergic complications				
Bronchial Asthma	667	16.4	2810	8.8
Atopic Dermatitis	1150	28.3	1539	4.8
Mother's history of allergic diseases	1391	34.2	7408	23.1
Annual house hold income				
>6 million JPY	1410	34.6	10 507	32.8
4-6 million JPY	1531	37.6	11 437	35.7
<4 million JPY	1129	27.7	10 104	31.5

	Mean ± SD	Mean ± SD
Mother's height [cm]	158.2 ± 5.2	158.3 ± 5.3
Mother's weight [cm]	52.3 ± 7.4	53.2 ± 8.6
Male		
height of birth [cm]	49.5 ± 1.8	49.6 ± 1.8
weight of birth [kg]	3.15 ± 0.34	3.14 ± 0.34
Female		
height of birth [cm]	49.1 ± 1.7	49.0 ± 1.8
weight of birth [kg]	3.08 ± 0.32	3.06 ± 0.32
Male		
Height at age 3 [cm]	92.1 ± 3.5	92.6 ± 3.4
Weight at age 3 [kg]	13.6 ± 1.4	13.8 ± 1.4
BMI at age 3 [kg/m2]	16.0 ± 1.2	16.1 ± 1.2
Female		
Height at age 3 [cm]	91.2 ± 3.4	91.5 ± 3.4
Weight at age 3 [kg]	13.2 ± 1.4	13.4 ± 1.4
BMI at age 3 [kg/m2]	15.9 ± 1.2	16.0 ± 1.3
Male		
Height SD score at age 3	−0.396 ± 0.994	−0.249 ± 0.951
Weght SD score at age 3	−0.009 ± 0.889	0.134 ± 0.879
BMI SD score at age 3	0.272 ± 0.656	0.314 ± 0.656
Female		
Height SD score at age 3	−0.202 ± 1.022	−0.091 ± 1.022
Weight SD score at age 3	0.016 ± 0.892	0.116 ± 0.889
BMI SD score at age 3	0.281 ± 0.630	0.308 ± 0.662

Table 1. Clinical Characteristics in each group. *JPY, Japanese yen*

Eliminated items[a]	Height				Weight			BMI		
	n	β	(95%CI)	P value	β	(95%CI)	P value	β	(95%CI)	P value
Male										
Egg	1849	−0.046	(−0.135, 0.043)	0.309	−0.061	(−0.143, 0.022)	0.148	−0.033	(−0.098, 0.032)	0.318
Milk	761	−0.097	(−0.175, −0.019)	0.015	−0.115	(−0.187, −0.043)	0.002	−0.044	(−0.101, 0.013)	0.128
Wheat	262	0.035	(−0.083, 0.153)	0.563	−0.019	(−0.128, 0.091)	0.740	−0.046	(−0.132, 0.041)	0.303
Soy	123	−0.307	(−0.474, −0.140)	<0.001	−0.116	(−0.270, 0.039)	0.143	0.092	(−0.030, 0.214)	0.140
Fish	177	0.095	(−0.044, 0.233)	0.179	0.104	(−0.025, 0.232)	0.113	0.037	(−0.064, 0.139)	0.470
Rice	15	−0.089	(−0.548, 0.370)	0.704	−0.189	(−0.614, 0.236)	0.383	−0.104	(−0.439, 0.232)	0.544
Fruit	145	−0.113	(−0.266, 0.040)	0.146	−0.170	(−0.312, −0.028)	0.019	−0.091	(−0.203, 0.021)	0.112
Food allergy	2336	−0.024	(−0.106, 0.057)	0.558	−0.028	(−0.104, 0.048)	0.472	−0.008	(−0.068, 0.052)	0.799
No food allergy	15 977	Reference			Reference			Reference		
Female										
Egg	1303	−0.042	(−0.145, 0.062)	0.428	−0.036	(−0.127, 0.055)	0.440	−0.008	(−0.079, 0.062)	0.818
Milk	494	−0.103	(−0.204, −0.002)	0.047	−0.114	(−0.203, −0.026)	0.012	−0.051	(−0.120, 0.018)	0.150
Wheat	134	0.029	(−0.146, 0.204)	0.745	0.041	(−0.112, 0.195)	0.597	0.022	(−0.097, 0.141)	0.716
Soy	67	0.131	(−0.112, 0.375)	0.290	0.127	(−0.087, 0.340)	0.246	0.053	(−0.114, 0.219)	0.536
Fish	119	0.033	(−0.147, 0.212)	0.720	0.051	(−0.106, 0.209)	0.524	0.023	(−0.099, 0.146)	0.707
Rice	8	−0.644	(−1.335, 0.047)	0.068	−0.693	(−1.299, −0.086)	0.025	−0.263	(−0.735, 0.209)	0.275
Fruit	119	−0.034	(−0.215, 0.147)	0.716	−0.025	(−0.184, 0.134)	0.761	−0.004	(−0.128, 0.119)	0.947
Food allergy	1734	−0.036	(−0.131, 0.059)	0.455	−0.034	(−0.117, 0.049)	0.422	−0.008	(−0.073, 0.056)	0.802

Table 2. Comparison of height and weight at age 3 (using Standard Deviation scores) among limited food items [a]*Eliminated items is defined when either of the following questions are satisfied: 'has never eaten', 'partial avoidance', 'has eaten before, however, now complete avoidance'.*

Eliminated items[a]	Height				Weight			BMI		
	n	β	(95%CI)	P value	β	(95%CI)	P value	β	(95%CI)	P value
Male										
Egg	1849	−0.062	(−0.149, 0.025)	0.164	−0.074	(−0.155, 0.007)	0.074	−0.058	(−0.090, −0.026)	<0.001
Milk	761	−0.115	(−0.191, −0.039)	0.003	−0.132	(−0.202, −0.061)	<0.001	−0.079	(−0.127, −0.031)	0.001
Wheat	262	−0.052	(−0.165, 0.060)	0.363	−0.091	(−0.195, 0.014)	0.089	−0.092	(−0.170, −0.013)	0.023
Soy	123	−0.335	(−0.494, −0.176)	<0.001	−0.179	(−0.327, −0.032)	0.017	0.009	(−0.105, 0.123)	0.877
Fish	177	0.021	(−0.113, 0.155)	0.760	0.031	(−0.094, 0.155)	0.630	−0.024	(−0.119, 0.072)	0.627
Rice	15	−0.277	(−0.720, 0.166)	0.221	−0.348	(−0.759, 0.063)	0.097	−0.172	(−0.496, 0.151)	0.297
Fruit	145	−0.140	(−0.287, 0.007)	0.062	−0.186	(−0.322, −0.050)	0.007	−0.123	(−0.228, −0.018)	0.022
Food allergy	2336	−0.102	(−0.142, −0.063)	<0.001	−0.123	(−0.160, −0.086)	<0.001	−0.051	(−0.080, −0.022)	0.001
No food allergy	15 977	Reference			Reference			Reference		
Female										
Egg	1303	−0.042	(−0.145, 0.061)	0.421	−0.036	(−0.126, 0.055)	0.438	−0.026	(−0.063, 0.012)	0.176
Milk	494	−0.105	(−0.203, −0.006)	0.037	−0.115	(−0.202, −0.029)	0.009	−0.059	(−0.118, 0.000)	0.048
Wheat	134	−0.019	(−0.185, 0.148)	0.824	−0.010	(−0.156, 0.137)	0.898	−0.017	(−0.127, 0.093)	0.761
Soy	67	0.050	(−0.180, 0.281)	0.668	0.047	(−0.155, 0.250)	0.649	0.005	(−0.151, 0.160)	0.952
Fish	119	0.015	(−0.161, 0.190)	0.871	0.033	(−0.121, 0.187)	0.674	−0.003	(−0.119, 0.114)	0.962
Rice	8	−0.604	(−1.258, 0.050)	0.070	−0.639	(−1.214, −0.065)	0.029	−0.253	(−0.699, 0.193)	0.267
Fruit	119	−0.058	(−0.234, 0.117)	0.515	−0.050	(−0.204, 0.105)	0.528	−0.032	(−0.149, 0.084)	0.588
Food allergy	1734	−0.092	(−0.140, −0.043)	<0.001	−0.086	(−0.129, −0.043)	<0.001	−0.025	(−0.058, 0.008)	0.143
No food allergy	16 071	Reference			Reference			Reference		

Table 3. The amount of change when each food item was avoided [a]*Eliminated items are defined when either of the following questions are satisfied: 'has never eaten', 'partial avoidance', 'has eaten before, however, 'now complete avoidance.*

Eliminated item[a]	Height				Weight			BMI		
	n	β	(95%CI)	P value	β	(95%CI)	P value	β	(95%CI)	P value
Male										
until 3y[a]	1166	−0.144	(−0.090, −0.199)	<0.001	−0.164	(−0.215, −0.114)	<0.001	−0.065	(−0.105, −0.025)	0.001
until 2y[b]	492	−0.070	(0.010, −0.149)	0.085	−0.116	(−0.190, −0.043)	0.002	−0.065	(−0.123, −0.007)	0.027
until 1.5y[c]	255	−0.063	(0.045, −0.172	0.252	−0.066	(−0.166, 0.035)	0.200	−0.030	(−0.109, 0.049)	0.461
Others[d]	122	−0.219	(−0.063, −0.375)	0.006	−0.215	(−0.359, −0.070)	<0.001	−0.064	(−0.178, 0.050)	<0.001
No food allergy	15 977	Reference			Reference			Reference		
Female										
until 3y[a]	760	−0.133	(−0.063, −0.204)	<0.001	−0.139	(−0.201, −0.077)	<0.001	−0.050	(−0.098, −0.002)	0.042
until 2y[b]	377	−0.078	(0.019, −0.175)	0.115	−0.058	(−0.143, 0.027)	0.181	−0.005	(−0.072, 0.061)	0.871
until 1.5y[c]	242	−0.027	(0.093, −0.147)	0.657	−0.080	(−0.186, 0.025)	0.134	−0.062	(−0.144, 0.019)	0.135
Others[d]	89	−0.068	(0.129, −0.264)	0.498	0.071	(−0.101, 0.244)	<0.001	0.113	(−0.022, 0.247)	<0.001
No food allergy	16 071	Reference			Reference			Reference		

Table 4. Association between height, weight at age 3 (using Standard Deviation scores) and duration of dietary elimination *[a]Eliminated items is defined when either of the following questions are satisfied: "has never eaten", "partial avoidance", "has eaten before, however, now complete avoidance". Duration of eliminated food until 3y was defined answering "Yes" in questionnaires asked every 6 months up to 3 years. [b]Answered "Yes" in questionnaires asked every 6 months up to 2 years. [c]Answered "Yes" in questionnaires asked every 6 months up to 1.5 years. [d]Others are defined as either cases: 1) Answered "Yes" only in the questionnaires at 1.5 years and 3 years, 2) Answered "Yes" only in the questionnaires at 2 years, 3) Answered "Yes" only in the questionnaires at 2 years and 3 years.*

	Height				Weight			BMI		
	n	β	(95%CI)	P value	β	(95%CI)	P value	β	(95%CI)	P value
Male										
Food Avoidance	2035	−0.155	(−0.101, −0.209)	<0.001	−0.182	(−0.231, −0.132)	<0.001	−0.076	(−0.115, −0.037)	<0.001
BA	428	−0.024	(0.030, −0.077)	0.385	0.091	(0.042, 0.141)	<0.001	0.106	(0.067, 0.146)	<0.001
Food Avoidance*BA		0.002	(0.055, −0.052)	0.949	0.024	(−0.026, 0.073)	0.349	0.023	(−0.016, 0.062)	0.247
Food Avoidance	2035	−0.121	(−0.071, −0.172)	<0.001	−0.127	(−0.174, −0.080)	<0.001	−0.044	(−0.082, −0.007)	0.019
AD	694	−0.136	(−0.085, −0.186)	<0.001	−0.078	(−0.125, −0.031)	0.001	0.013	(−0.024, 0.050)	0.492
Food Avoidance*AD		0.001	(0.051, −0.050)	0.979	−0.018	(−0.065, 0.029)	0.457	−0.017	(−0.054, 0.020)	0.378
Female										
Food Avoidance	1468	−0.147	(−0.072, −0.222)	<0.001	−0.165	(−0.230, −0.099)	<0.001	−0.068	(−0.119, −0.016)	0.010
BA	239	−0.055	(0.020, −0.130)	0.150	0.049	(−0.017, 0.115)	0.145	0.080	(0.029, 0.131)	0.002
Food Avoidance*BA		0.029	(0.104, −0.045)	0.442	0.057	(−0.009, 0.123)	0.089	0.037	(−0.014, 0.088)	0.157
Food Avoidance	1468	−0.094	(−0.030, −0.157)	0.004	−0.119	(−0.175, −0.063)	<0.001	−0.055	(−0.099, −0.011)	0.014
AD	456	−0.128	(−0.064, −0.192)	<0.001	−0.140	(−0.196, −0.084)	<0.001	−0.059	(−0.103, −0.016)	0.008
Food Avoidance*AD		−0.008	(0.056, −0.071)	0.817	0.050	(−0.006, 0.106)	0.083	0.052	(0.008, 0.095)	0.020

Table 5. Interaction between food avoidance and allergic complications on height/weight at age 3 using Standard Deviation scores *BA, Bronchial asthma; AD, Atopic dermatitis.*

Household income	n	Height			Weight		BMI		
		β	(95%CI)	P value	(β 95%CI)	P value	β	(95%CI)	P value
Male									
>6 million JPY	805	−0.070	(0.118 , −0.259)	0.463	(−0.143-0.315 , 0.029)	0.103	−0.096	(−0.226 , 0.033)	0.145
4–6 million JPY	897	−0.048	(0.128 , −0.223)	0.596	(−0.115-0.275 , 0.046)	0.162	−0.084	(−0.210 , 0.043)	0.195
<4 million JPY	634	−0.302	(−0.092 , −0.512)	0.005	(−0.208-0.397 , −0.019)	0.031	−0.020	(−0.174 , 0.134)	0.802
Female									
>6 million JPY	605	−0.109	(0.088 , −0.306)	0.279	(0.019-0.150 , 0.188)	0.825	0.081	(−0.044 , 0.206)	0.203
4–6 million JPY	634	−0.029	(0.184 , −0.242)	0.792	(−0.084-0.273 , 0.105)	0.382	−0.074	(−0.218 , 0.070)	0.316
<4 million JPY	495	0.052	(0.293 , −0.189)	0.673	(−0.105-0.318 , 0.107)	0.331	−0.121	(−0.273 , 0.032)	0.122

Table 6. Association between food avoidance and height/weight at age 3 (using Standard Deviation scores) stratifeid by annual household income among subjects with food allergy
JPY, Japanese yen.

while females were more prevalent in the ≥18-year-old group.[3] Causal ingredients vary widely with age. Causative foods responsible for over 5% of morbidities were: 0-year-old (eggs 60.6%, milk 24.8%, wheat 10.8%), 1–2-year-olds (eggs 36.3%, milk 17.6%, nuts 15.4%, fish eggs 8.2%, peanuts 6.6%, wheat 5.8%), 3-6-year-olds (nuts 27.8%, milk 16.0%, eggs 14.7%, peanuts 12.0%, fish eggs 10.3%, wheat 6.7%). Fruits cause immediate allergic reactions less than 5% in ages 0–3 years. Soybeans ranked tenth in the list of food items, accounting for 1.3% of FAs, while rice and fish did not figure in the top 10.[3] Rice, fish, and soybeans are basic ingredients in a Japanese meal. Based on this, we considered them to be an important factor affecting body size. Nuts, including peanuts, are one of the top foods causing FAs but in Japan, there is no particular culture of eating nuts during early childhood. Besides, nuts are associated with a high risk of aspiration in infancy. Therefore, a large number of respondents answered that they did not eat nuts even though they did not suffer from FA. Avoidance of nuts was unlikely to affect children body size; hence nuts were excluded from the list of evaluated food items. Fish eggs were unfortunately not on the questionnaire of the JECT study.

Several reports indicate that milk avoidance causes growth retardation. Robbins et al documented decreased height, weight, BMI, and total caloric intake in 6189 children with milk allergy aged 2–17 years.[5] Jensen et al found that eliminating milk due to milk allergy for 4 years exhibited decreased bone density and an approximate 1.4-year average delay in bone age when compared with healthy children.[6] In 253 children aged >2 years, Yanagida et al reported a significant increase in height when milk restriction was lifted 1 year after FA diagnosis. The authors noted that it is crucial to prioritize lifting restrictions on milk consumption for multiproduct FAs.[14]

The nutritional significance depends on the dietary culture of the population being examined. The nutritional importance of soy in Japan differs from that in Western countries, as Japan is known to consume more soybeans than other countries.[15] Furthermore, nutritional significance changes with age. A population-based cohort study of 3564

subjects found that the dietary intake of protein at age 1 year was associated with growth trajectories of height, weight, and BMI between the ages of 1 and 9 years.[16] In Japan, protein-rich nutrition intake under the age of 5 years includes 250 g of dairy products, 40–60 g of soybeans, 30 g of eggs, and 50 g of meat and fish.[17] However, after the age of 6 years, the intake includes 250–320 g of dairy products, 80 g of soybeans, 50 g of eggs, and 80–180 g of meat and fish.[17] Although the consumption of dairy products remained nearly unaltered, the consumption of meat and fish tripled. Soybeans provide a relatively high proportion of protein to Japanese preschoolers. In Japan, soybean is consumed in the form of tofu. Tofu is soft, easy to process, and likely to be added to dishes as a protein source, especially during weaning when the chewing ability is relatively lower. Soy isoflavone has been reported to promote osteoblast maturation and mineralization. It can also inhibit osteoclast bone resorption and promote bone formation.[18] This could be an underlying factor for low height SD in males.

To our knowledge, fruit avoidance has not been reported as a cause of growth failure. Fruit may be used as a complementary food, and thus, their avoidance causes low body weight owing to the missing calories. However, further investigations are required.

Rice is the staple food of Japan and is generally consumed daily. Although no significant difference was observed, rice avoidance in males had the largest beta value in weight SD and BMI-SD among the seven food items. These results may be partly explained by the small number of participants who avoided rice (male: $n = 15$; female: $n = 8$).

Intervention by a nutritionist may be effective to reduced growth retardation.[7] However, in this study, there was no question asking whether a nutritionist's guidance was obtained. In addition, the concomitant use of breast milk or allergy formula may supplement deficient nutrients. However, the presence or absence of their use and the duration of their use were not included in the questionnaire and are unknown in this study.

Our study also revealed that the period of food avoidance is important (Table 4); longer periods of food avoidance have a relatively greater impact. Isolauri et al. reported decreased mean length SD score and weight-for-length index even at the age of 1 year in the case of milk allergy.[13] Food avoidance should be ended at the earliest (Table 4).

Gender-based differences in the incidence of allergic diseases have been observed. Before puberty, BA, AD, and FA are predominant in males,[19] as in our study. These chronic diseases cause high-energy expenditure, which may affect growth. In a study of 6377 oral food challenge tests in children with FA in which 85% were under the age of 18 years, males were reported to develop symptoms 16% more often.[20] In younger age groups, males may have more severe phenotypes, which may lead to more severe or prolonged food restriction. A combination of the above factors may explain why males have a more severe growth failure than females. Therefore, young males should be monitored carefully.

Several reports have shown that AD results in growth impairment, which was also observed in our study; Beck et al found that patients were underweight, short-statured, at 1 year of age.[21] Jhamnani et al reported that children with AD and milk restriction were short-statured.[22] Age-specific prevalence of AD in Japan is known to be 9.8% at 1.5 years and 13.2% at 3 years.[23] Another JECS birth cohort study found that continuous AD with onset at <1 year of age had the strongest incidence of developing FA at age 3 years.[24] Damaged skin barrier seen in AD can be a risk factor for food sensitization development and FA. Additionally, lack of sleep due to itching and increased metabolic demands due to accelerated skin turnover are associated factors that may inhibit growth.

In our study, an interaction between atopic dermatitis and food allergy on BMI-SD in females were significant at age 3 years.

FA incurs direct, indirect, and intangible costs. Frykas et al conducted a cross-sectional study of 63 parents of children with FA. There was 14.3% of parents reporting career limitations, and 28.6% were below Canada's after-tax-low-income cutoff level.[25] Wai et al also reported increased expenditures and decreased income associated with child hospitalization were found in the 0–12-year-old pediatric FA group.[26] Low income may

simply restrict the supply of adequate food alternatives. Furthermore, gender differences in our results may be because males had more FA items and more complications of allergic diseases.

Recent reviews indicate that food-allergic children tend to have lower growth parameters and are particularly impaired in height for age.[4] But FA can have spontaneous remission. And oral immunotherapy is also now widely used as a treatment method in our country. There is still a paucity of literature that discusses how the growth will be in children who have acquired tolerance and then become able to consume the responsible food. In a Finnish nested case-control study, despite having a balanced diet with adequate energy and protein, children with milk elimination for at least 1year had lower SD in height with no catch-up growth by the age of 5 years.[27]

In another Japanese study, a questionnaire survey was conducted among 7–15 years old children in 30 elementary schools in Kyoto.[28] They asked parents to evaluate their children's height and weight in relation to their elimination of wheat, milk, and eggs due to immediate-type FA. The results showed that there was no difference in height and weight at age 6 if the children had acquired tolerance by age 3. However, if the child had eliminated milk by age 3 or had eliminated 2 or more of the 3 kinds of food, the height was lower at age 6. Weight was also lower for those with FA continuing after age 3.[28] Although our study did not investigate whether growth catches up, the JECS survey continues after age 3, and we are looking forward to further results from this survey.

The strength of this study was its large sample size (36 118 participants). However, this study had several limitations. Only the mother's height and weight were used as a covariate in this study as the father's height and weight were not measured. Patient information was collected using a questionnaire, and oral food, blood, and prick tests were not conducted simultaneously. Owing to the questionnaire format, prevalence rate may appear to be higher than the actual one. The allergy types (IgE or non-IgE type) were not identified. Our study did not define food avoidance as complete elimination, which includes a wide range of degrees of elimination.

In conclusion, children with FA who avoided food revealed a significantly lower SD score on height and weight at age of 3 years. Although food avoidance is necessary for patients with FA, physicians should be aware of the potential growth impairment and restrict food avoidance to short periods. Key nutrients may differ according to age and culture conditions. Milk and soy were important factors in our study. Prolonged food avoidance impairs growth at age 3 years. Gender differences must also be taken into consideration, and prevalence of allergic diseases such as FA, AD, BA were higher in males. When it comes to age <3 years, males require more careful observation.

Abbreviations

FA; Food allergy, FAs; Food allergies, JECS; Japan Environment and Children's Study, LMS; Lambda-mu-sigma, ANOVA; analysis of variance, SD; standard deviation, CI; confidence interval, BA; bronchial asthma, AD; atopic dermatitis, JPY; Japanese yen

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Data availability
"Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amendment on September 9, 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies."

Authors' contributions
MS designed the study, collected and interpreted the data, and wrote the manuscript. HH and MSh performed the statistical analysis and interpreted the data. MO, TF, AH, YT and MSh interpreted the data, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Ethics statement
The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions. Written informed consent was obtained from all the participants.

Consent for publication
All authors indicated consent for publication in the journal.

Declaration of competing interest
The authors have no conflict of interest to declare.

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REFERENCES

1. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72:1133–1147.
2. Yamamoto K, Pak K, Saito M, et al. *Allergy and Immunology in Young Children of Japan: The JECS Cohort*. vol. 13. World Allergy Organization; 2020.
3. Imai T, Sato S, Sugisaki C, Ebisawa M. Customers affair agency government of Japan. Report on Research and Study Project on Food Labeling Related to Food Allergy in 2021. https://www.caa.go.jp/policies/policy/food_labeling/food_sanitation/allergy/assets/food_labeling_cms204_220601_01.pdf Accessed April 21, 2023.
4. Meyer R. Nutritional disorders resulting from food allergy in children. *Pediatr Allergy Immunol*. 2018;29:689–704.
5. Robbins KA, Wood RA, Keet CA. Milk allergy is associated with decreased growth in US children. *J Allergy Clin Immunol*. 2014;134:1466–1468.
6. Jensen VB, Jørgensen IM, Rasmussen KB, Mølgaard C, Prahl P. Bone mineral status in children with cow milk allergy. *Pediatr Allergy Immunol*. 2004;15:562–565.
7. Kawamoto T, Nitta H, Murata K, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Publ Health*. 2014;14:25.
8. Isojima T, Kato N, Ito Y, Kanzaki S, Murata M. Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. *Clin Pediatr Endocrinol*. 2016;25:71–76.
9. Kato N, Takimoto H, Sudo N. The cubic function for spline smoothed L,S and M values for BMI reference data of Japanese children. *Clin Pediar Endocrinol*. 2011;20:47–49.
10. Weiland SK, Björkstén B, Brunekreef B, et al. Phase II of the international study of asthma and allergies in childhood (ISAAC II): rationale and methods. *Eur Respir J*. 2004;24:406–412.
11. Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8:483–491.
12. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, ISAAC Steering Committee. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tubercul Lung Dis*. 2005;9:10–16.
13. Isolauri E, Sütas Y, Salo M, Isosomppi R, Kaila M. Elimination diet in cow's milk allergy: risk for impaired growth in young children. *J Pediatr*. 1998;132:1004–1009.
14. Yanagida N, Minoura T, Kitaoka S. Does terminating the avoidance of cow's milk lead to growth in height? *Int Arch Allergy Immunol*. 2015;168:56–60.
15. International comparison of soybean consumption (2007) Data source FAO STAT Food supply. https://www.otsuka.co.jp/en/nutraceutical/about/soylution/encyclopedia/consumption.html. Accessed May 11, 2023.
16. Braun KV, Erler NS, Kiefte-de Jong JC, et al. Dietary intake of protein in early childhood is associated with growth trajectories between 1 and 9 Years of age. *J Nutri*. 2016;146:2361–2367.
17. Kagawa Y. Total Guide of Japanese Food Composition 2017 Food composition by age, sex, and physical activity level, divided by four food groups. https://www.jikkyo.co.jp/contents/download/9992659259. Accessed June 16, 2022.
18. Ming LG, Chen KM, Xian CJ. Functions and action mechanisms of flavonoids genistein and icariin in regulating bone remodeling. *J Cell Physiol*. 2013;228:513–521.

19. Pali-Schöll I, Jensen-Jarolim E. Gender aspects in food allergy. *Curr Opin Allergy Clin Immunol*. 2019;19:249–255.

20. Akuete K, Guffey D, Israelsen RB, et al. Multicenter prevalence of anaphylaxis in clinic-based oral food challenges. *Ann Allergy Asthma Immunol*. 2017;119:339–48e1.

21. Beck C, Koplin J, Dharmage S, et al. Persistent food allergy and food allergy coexistent with eczema is associated with reduced growth in the first 4 Years of life. *J Allergy Clin Immunol Pract*. 2015;4:248–256.

22. Jhamnani RD, Levin S, Rasooly M, et al. Impact of food allergy on the growth of children with moderate-severe atopic dermatitis. *J Allergy Clin Immunol*. 2018;141:1526, 9.e4.

23. Yamamoto S. [Study on the Actual Number of Patients with Atopic Dermatitis and the Environmental Factors Affecting the Onset and Exacerbation of the Disease:Summary Report of 2002 Research Project:Prevention and Treatment of Immunological Allergic Diseases Funded by Scientific Grant from the Ministry of Health,Labour,and Welfare.] (in Japanese) https://mhlw-grants.niph.go.jp/system/files/2002/000227/200200824A/200200824A0001.pdf. Accessed June 16, 2022.

24. Yamamoto K, Suzuki Y, Yang L, et al. Persistent eczema leads to both impaired growth and food allergy: JECS birth cohort. *PLoS One*. 2021;1:1–9.

25. Frykas TLM, Golding M, Abrams EM, Simons E, Protudjer JLM. Mothers of children with food allergies report poorer received life status which may be explained by limited career choices. *Allergy Asthma Clin Immunol*. 2021;17:1–4.

26. Wai HM, Middelveld R, Thörnqvist V, et al. Pediatric food allergy-related household costs are influenced by age, but not disease severity. *World Allergy J*. 2019;12:1–7.

27. Tuokkola J, Luukkainen P, Nevalainen J, et al. Eliminating cows' milk,but not wheat,barley or rye,increases the risk of growth deceleration and nutritional inadequacies. *Acta Pediatrica*. 2017;106:1142–1149.

28. Mukaida K, Kusunoki T, Morimoto T, et al. The effect of past food avoidance due to allergic symptoms on the growth of children at school age. *Allergol Int*. 2010;59:369–374.