



Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com



Yogurt consumption in infancy is inversely associated with atopic dermatitis and food sensitization at 5 years of age: A hospital-based birth cohort study

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ARTICLE INFO

Article history:

Received 29 September 2016

Received in revised form 20 December 2016

Accepted 4 January 2017

Keywords:

Atopic dermatitis

Birth cohort

Children

Sensitization

Yogurt

ABSTRACT

Background: Several studies have suggested that habitual yogurt consumption is associated with favorable outcomes for health issues in children. However, the effects of yogurt consumption on allergic diseases and sensitization in children remain poorly understood.

Objective: This prospective birth cohort study aimed to investigate for associations between habitual yogurt consumption in infancy and development of allergic diseases/sensitization at 5 years of age.

Methods: Data were obtained from the Tokyo Children's Health, Illness and Development (T-CHILD) study. A total of 1550 children were born to the recruited women. Consumption of yogurt by children during infancy was determined by using questionnaires completed at 12 months of age. Outcome data for children were collected from the questionnaires and medical check-ups completed at 5 years of age. Possible associations between habitual yogurt consumption in infancy and allergic diseases/sensitization were analyzed by multiple logistic regression analyses.

Results: We analyzed the data for 1166 children whose parents responded at 5 years of age. Habitual yogurt consumption in infancy and atopic dermatitis at 5 years of age were significantly associated (UKWP criteria: aOR, 0.70; 95% CI, 0.51–0.97; $P=0.03$). Children with habitual yogurt consumption in infancy were less likely to be sensitized to food allergens (aOR, 0.53; 95% CI, 0.31–0.93; $P=0.03$), but no associations were seen in regard to any other allergens.

Conclusions: Our study demonstrated that habitual consumption of yogurt in infancy has the potential to prevent development of atopic dermatitis and food sensitization, but not other allergic diseases, at 5 years of age.

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1. Introduction

The increasing prevalence of allergic diseases, especially in westernized countries, is becoming a public health burden. One of the leading theories to explain the modern-day allergy epidemic was proposed by Strachan in 1989, namely, the hygiene hypothesis [1]. Drawing on the hygiene hypothesis, the apparent rise in the prevalence of allergic diseases might be due to reduced early-life

environmental exposure to microorganisms, with consequent alteration in the balance of the immune response [2].

Growing evidence supports a pivotal role for infant gut colonization in the development of the immune system [3]. A decrease in certain microbes such as lactobacilli and/or gut microbiota diversity, especially during early childhood, seems to be associated with subsequent development of allergic diseases [4]. In this context, manipulation of the intestinal microbiota by probiotic

Abbreviations: T-CHILD, Tokyo Children's Health, Illness and Development; OR, odds ratio; CI, confidence interval; ISAAC, International Studies of Asthma and Allergies in Childhood; UKWP, United Kingdom Working Party.

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<http://dx.doi.org/10.1016/j.jdermsci.2017.01.006>

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Please cite this article in press as: T. Shoda, et al., Yogurt consumption in infancy is inversely associated with atopic dermatitis and food sensitization at 5 years of age: A hospital-based birth cohort study, J Dermatol Sci (2017), <http://dx.doi.org/10.1016/j.jdermsci.2017.01.006>

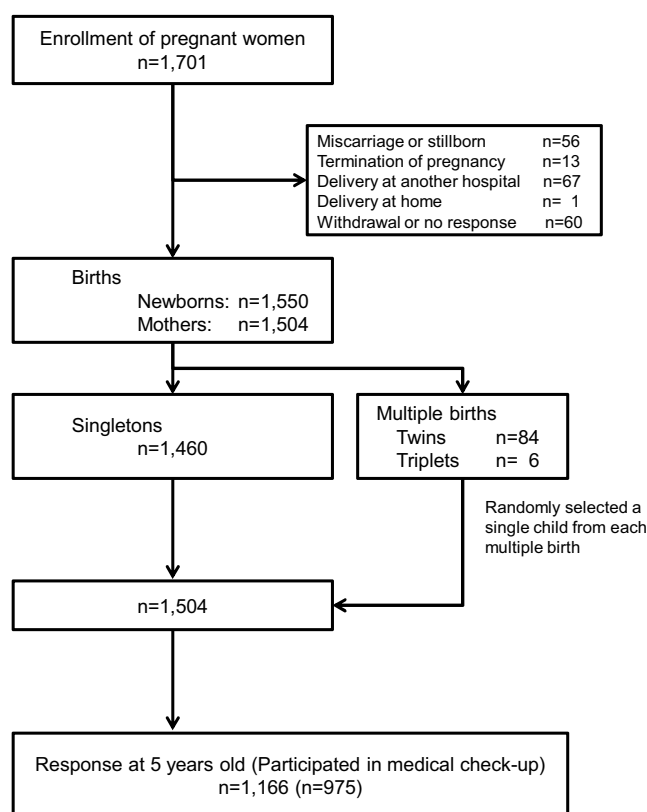


Fig. 1. Flow chart of the study population.

supplementation has been thought to be potentially beneficial in prevention of allergic diseases. Indeed, recent systematic reviews and meta-analyses of randomized controlled trials showed that probiotics used by pregnant women or breastfeeding mothers and/or given to infants at high risk of allergic diseases reduced the infants' risk of atopic dermatitis/eczema, but not other allergic diseases [5,6]. However, it is still uncertain whether these strategies would protect against allergic diseases in an unselected population (i.e., children both with and without a parental history of allergic diseases).

Yogurt, one of the best-known foods that contain probiotics, is produced by culturing dairy ingredients with lactic acid bacteria [7]. Yogurt consumption, probably through its effect on the gut microbiota, was associated with favorable outcomes for health issues in children [8]. As for allergic diseases, Roduit et al. investigated for an association between introduction of yogurt in the first year of life and the protective effect against atopic dermatitis [9]. Notably, they showed promising and intriguing results that early introduction of yogurt prevented atopic dermatitis, with statistical significance (odds ratio 0.41; 95% CI, 0.23–0.73). However, they investigated only the effect on atopic dermatitis, not on other allergic diseases or allergic sensitization. Our analysis using the data from a prospective birth cohort study aimed to investigate for associations between habitual yogurt consumption in infancy and development of allergic diseases and sensitization.

2. Materials and methods

2.1. Study design and population

The Tokyo Children's Health, Illness and Development (T-CHILD) study, also known as the "Seiiku Cohort Study", was a single-center, prospective, hospital-based birth cohort study. The

design of this study has been described in detail elsewhere [10]. Briefly, the T-CHILD study enrolled 1701 pregnant women under 16 weeks' gestation from the National Center for Child Health and Development (NCCHD), Tokyo, Japan between October 2003 and December 2005. A total of 1550 children were born to the recruited women between March 2004 and August 2006. In the case of multiple births in this study population, we randomly selected one of the children for inclusion in the analysis. For the examination at 5 years of age, 1166 mothers of children responded to the questionnaire, and 975 children participated in the medical check-up. Data with missing values were deleted when fitting to the models.

2.2. Questionnaire

Data from surveys conducted during maternal pregnancy and when children were 12 months and 5 years of age were analyzed in this study.

Consumption of dietary yogurt by the children during infancy was determined based on the reply to the following question at 12 months of age: "Over the past 12 months, how often did your child eat yogurt, lactobacillus-fermented milk or products?" The intake frequencies of yogurt were classified into three groups as a dietary habit during infancy: 1) none, 2) sometimes, and 3) every day. A response of "3) every day" was considered to be habitual yogurt consumption.

Allergic diseases were investigated using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which was completed by parents when their children were 5 years old [11] (Table E1). The ISAAC questionnaire was translated into Japanese and validated. Additionally, we collected the data on atopic dermatitis, which was formally diagnosed using the United Kingdom Working Party (UKWP)'s diagnostic criteria [12] at medical check-up at 5 years of age.

Variables considered to be potential confounders were as follows: parental history of allergic disease, gender, preterm birth, mode of delivery, season of birth, smoking during pregnancy and pet ownership during pregnancy. Data on those variables were obtained from questionnaires completed at 16, 23 and 34 weeks' gestation and the medical charts. Data on breast feeding, timing of solid food introduction, history of food allergy until 1 year, history of wheeze until 1 year, history of eczema until 1 year, number of previous live births and daycare during infancy were obtained from questionnaires completed at 12 months of age.

2.3. Sensitization

Serum samples were obtained from participants at 5 years of age, and aliquots were frozen and stored at -30°C until assay. Specific IgE concentrations in serum samples were determined using the molecular multiplex test ImmunoCAP[®] ISAC (Thermo Fisher Scientific, Uppsala, Sweden), [13,14]. Sensitization was defined as a positive result for any single allergen if a specific IgE level of ≥ 0.3 ISAC standardized units (ISU) was observed. The sensitizing antigens (103) are shown in Table E2 and include 40 food allergens and 53 inhalant allergens, plus 10 miscellaneous allergens.

2.4. Statistical analysis

Differences in the characteristics of children stratified as to habitual yogurt consumption in infancy were tested as categorical variables using the chi-square test. We built logistic models to estimate associations between habitual yogurt consumption in infancy and allergic diseases in children at 5 years of age. We built the models as follows: first, we fitted model 1 with all the potential

Table 1
Characteristics of child participants.

		n	%
<i>Independent variables^a</i>			
Parental history of allergic diseases	no	251	22.6
	yes	860	77.4
	missing values	55	
Gender	boy	590	50.6
	girl	576	49.4
	missing values	0	
Preterm birth	≥37 weeks	1082	92.8
	<37 weeks	84	7.2
	missing values	0	
Cesarean section	no	887	76.3
	yes	275	23.7
	missing values	4	
Season of birth	spring-summer	565	48.5
	fall-winter	600	51.5
	missing values	1	
Smoking during pregnancy	no	1139	98.0
	yes	23	2.0
	missing values	4	
Pet ownership during pregnancy	no	320	27.4
	yes	846	72.6
	missing values	0	
Breast feeding	0-5 month	172	15.1
	≥6 month	966	84.9
	missing values	28	
Timing of solid food introduction	<6 month	525	46.2
	≥6 months	612	53.8
	missing values	29	
History of food allergy until 1year	no	1017	90.8
	yes	103	9.2
	missing values	46	
History of eczema until 1year	no	254	22.3
	yes	884	77.7
	missing values	28	
History of wheeze until 1year	no	909	80.1
	yes	226	19.9
	missing values	31	
Number of previous livebirths	0	674	57.9
	≥1	491	42.1
	missing values	1	
Daycare during infancy	no	903	79.6
	yes	232	20.4
	missing values	31	
Habitual yogurt consumption in infancy	no	704	62.0
	no yogurt intake	87	
	sometimes	617	
	yes	432	38.0
	everyday	432	38.0
	missing values	30	
<i>Outcome based on questionnaire at 5 years of age^a</i>			
Ever wheeze	no	825	70.8
	yes	340	29.2
	missing values	1	
Current wheeze	no	969	83.2
	yes	195	16.8
	missing values	2	
Ever asthma	no	995	85.3
	yes	171	14.7
	missing values	0	
Current asthma	no	1055	90.5
	yes	111	9.5
	missing values	0	
Ever atopic dermatitis	no	868	76.1
	yes	272	23.9
	missing values	26	
Current atopic dermatitis	no	907	78.0
	yes	256	22.0
	missing values	3	
Ever rhinitis	no	725	62.2
	yes	440	37.8
	missing values	1	
Current rhinitis	no	1041	89.5
	yes	122	10.5
	missing values	3	

Table 1 (Continued)

		n	%
<i>Outcome based on medical check-ups at 5 years of age^b</i>			
Atopic dermatitis (UKWG)	no	675	69.2
	yes	300	30.8
<i>Sensitization</i>			
Any	negative	405	42.3
	at least 1 positive	552	57.7
	missing values	18	
Foods	negative	873	91.2
	at least 1 positive	84	8.8
	missing values	18	
Inhalants	negative	414	43.3
	at least 1 positive	543	56.7
	missing values	18	

^a N = 1166, including those whose parent responded to the questionnaire at 5 years of age.^b N = 975, including those whose parent responded questionnaire at 5 years of age and who participated in the medical check-up at 5 years of age.

confounders described above except allergic diseases until 1 year; then we added history of food allergy at 1 year to build model 2; we further added history of eczema at 1 year for model 3; and finally, history of wheeze at 1 year was added to develop model 4. In models 3 and 4, history of eczema at 1 year was not used as a covariant for modeling the probability of ever atopic dermatitis at 5 years of age, and history of wheeze at 1 year was not used as a covariant for modeling the probabilities of ever wheeze and ever asthma at 5 years of age. All tests were performed using SPSS version 22 (IBM Corp., Armonk, NY) with a 2-sided 5% significance level.

2.5. Ethical approval

This study was approved by the Ethics Committee of the National Center for Child Health and Development (Acceptance Number #52).

3. Results

3.1. Characteristics and prevalence of allergic diseases

Fig. 1 shows a flowchart of the study population. We obtained data for 1166 children whose parents responded to the questionnaire at 5 years of age. Table 1 shows the characteristics of the

Table 2

Associations of consumption of yogurt in infancy with allergy outcomes in children at 5 years of age.

	Model 1			Model 2			Model 3			Model 4		
	aOR ^a	95%CI	p	aOR ^b	95%CI	p	aOR ^c	95%CI	p	aOR ^d	95%CI	p
<i>ISAAC questionnaire^e</i>												
Ever wheeze	0.91	0.69–1.21	0.53	0.91	0.68–1.21	0.52	0.92	0.69–1.22	0.54	0.92	0.69–1.22	0.54
Current wheeze	1.06	0.75–1.50	0.74	1.04	0.74–1.48	0.81	1.05	0.74–1.49	0.78	1.07	0.75–1.52	0.72
Ever asthma	0.79	0.54–1.13	0.20	0.78	0.54–1.14	0.20	0.79	0.54–1.15	0.22	0.79	0.54–1.15	0.22
Current asthma	0.90	0.58–1.39	0.63	0.89	0.57–1.39	0.60	0.89	0.57–1.40	0.63	0.88	0.56–1.38	0.58
Ever atopic dermatitis	0.77	0.57–1.05	0.10	0.78	0.57–1.08	0.13	0.78	0.57–1.08	0.13	0.80	0.58–1.10	0.16
Current atopic dermatitis	0.72	0.53–0.99	0.04	0.71	0.52–0.99	0.04	0.72	0.52–0.99	0.05	0.73	0.52–1.01	0.06
Current atopic dermatitis ^g	0.70	0.50–1.00	0.05	0.69	0.48–0.99	0.04	0.68	0.47–0.99	0.04	0.69	0.48–0.99	0.05
Ever rhinitis	1.00	0.77–1.30	0.99	0.99	0.76–1.30	0.96	1.00	0.76–1.32	0.99	1.01	0.77–1.33	0.94
Current rhinitis	0.81	0.52–1.25	0.34	0.75	0.48–1.18	0.21	0.76	0.49–1.19	0.24	0.78	0.50–1.22	0.28
<i>UK Working Party Diagnostic Criteria^f</i>												
Atopic dermatitis up to 5 years old	0.73	0.54–0.99	0.04	0.70	0.51–0.96	0.03	0.70	0.51–0.97	0.03	0.70	0.51–0.97	0.03
Atopic dermatitis up to 5 years old ^g	0.72	0.52–1.02	0.06	0.69	0.48–0.97	0.04	0.69	0.48–0.98	0.04	0.69	0.48–0.98	0.04
<i>Sensitization^f</i>												
Any	0.83	0.62–1.11	0.21	0.84	0.63–1.12	0.24	0.85	0.63–1.14	0.27	0.84	0.63–1.13	0.25
Foods	0.55	0.33–0.94	0.03	0.54	0.31–0.93	0.03	0.54	0.31–0.93	0.03	0.53	0.31–0.93	0.03
Foods ^g	0.54	0.29–0.98	0.04	0.50	0.27–0.95	0.03	0.50	0.26–0.94	0.03	0.51	0.27–0.96	0.04
Inhalants	0.84	0.63–1.12	0.22	0.85	0.63–1.13	0.26	0.85	0.64–1.15	0.29	0.85	0.63–1.14	0.27

^a Model 1: Adjusted for parental history of allergic diseases, gender, preterm birth, mode of delivery, season of birth, smoking during pregnancy, pet ownership, breast feeding, timing of solid food introduction, number of previous live births, daycare during infancy.^b Model 2: Independent variables in model 1 plus history of food allergy at 1 year.^c Model 3: Independent variables in model 2 plus history of eczema at 1 year. History of eczema at 1 year was not used as a covariant for modeling probability of ever atopic dermatitis.^d Model 4: Independent variables in model 3 plus history of wheeze at 1 year. History of eczema at 1 year was not used as a covariant for modeling probability of ever atopic dermatitis, and history of wheeze at 1 year was not used as covariant for modeling probability of ever wheeze and ever asthma.^e Including those whose parent responded to the questionnaire at 5 years of age; missing data were excluded.^f Including those whose parent responded to the questionnaire at 5 years of age and participated in the medical check-up at 5 years of age; missing data were excluded.^g For children with allergic parents.

Table 3

Associations between the frequency of consumption of yogurt in infants and development of atopic dermatitis and sensitization to food.

	Model 1			Model 2			Model 3			Model 4		
	aOR ^a	95%CI	p	aOR ^b	95%CI	p	aOR ^c	95%CI	p	aOR ^d	95%CI	p
Current atopic dermatitis (ISAAC) ^e												
None	1			1			1			1		
Sometimes	0.50	0.30–0.82	0.006	0.59	0.32–0.90	0.018	0.50	0.29–0.84	0.009	0.48	0.28–0.82	0.007
Every day	0.40	0.23–0.67	0.001	0.42	0.24–0.72	0.002	0.39	0.22–0.68	0.001	0.39	0.22–0.68	0.001
p trend			0.002			0.004			0.003			0.003
None	1			1			1			1		
Sometimes	0.73	0.42–1.26	0.252	0.79	0.45–1.40	0.423	0.73	0.41–1.32	0.301	0.73	0.41–1.33	0.306
Every day	0.55	0.31–0.97	0.040	0.57	0.31–1.02	0.06	0.53	0.29–0.98	0.044	0.53	0.29–0.99	0.046
p trend			0.021			0.018			0.017			0.018
Sensitization to foods ^f												
None	1			1			1			1		
Sometimes	0.30	0.15–0.61	0.001	0.36	0.19–0.74	0.005	0.35	0.17–0.74	0.004	0.34	0.16–0.68	0.003
Every day	0.21	0.10–0.44	<0.001	0.23	0.11–0.51	<0.001	0.22	0.10–0.49	<0.001	0.21	0.09–0.47	<0.001
p trend			<0.001			0.001			0.001			0.001

^a Model 1: Adjusted for parental history of allergic diseases, gender, preterm birth, mode of delivery, season of birth, smoking during pregnancy, pet ownership, breast feeding, timing of solid food introduction, number of previous live births, daycare during infancy.

^b Model 2: Independent variables in model 1 plus history of food allergy at 1 year.

^c Model 3: Independent variables in model 2 plus history of eczema at 1 year.

^d Model 4: Independent variables in model 3 plus history of wheeze at 1 year.

^e Including those whose parent responded to the questionnaire at 5 years of age; missing data were excluded.

^f Including those whose parent responded to the questionnaire at 5 years of age and participated in the medical check-up at 5 years of age; missing data were excluded.

children in this analysis (the characteristics of children who were lost to follow-up are shown in Supplementary Table E3 in this article's Online Repository). The mothers of 38% of the children answered that their child ate yogurt habitually. In the stratification for habitual yogurt consumption in infancy, significant differences were detected only in terms of the number of previous live births and daycare during infancy (Table E4). Table 1 also shows the prevalences of allergic diseases based on the ISAAC questionnaire. The prevalence of atopic dermatitis was 22.0% based on ISAAC, and 30.8% based on the UKWP criteria. Data from 975 children at 5 years of age for whom there were results for the specific IgE concentrations showed that 57.7% of the children were sensitized to any one of the total allergens (103), 56.7% to inhalant allergens, and 8.8% to food allergens.

3.2. Association between habitual yogurt consumption in infancy and allergic diseases and sensitization at 5 years of age

To clarify whether habitual yogurt consumption in infancy affects the prevalence of allergy outcomes at 5 years old, multivariate logistic regression models were constructed for each allergy outcome, respectively. After adjustment for confounders, there was a significant association between habitual yogurt consumption in infancy and atopic dermatitis (UKWP criteria, aOR in model 4: 0.70; 95% CI, 0.51–0.97; $P=0.034$), but not other allergy outcomes, at 5 years of age (Table 2). Children with habitual yogurt consumption in infancy were significantly less likely to have positive sensitization to foods (aOR in model 4: 0.53; 95% CI, 0.31–0.93; $P=0.026$), but not to any one of the total allergens or inhalant allergens (Table 2).

We also performed a sub-analysis for children with allergic parents. The results were similar. Among the children with allergic parents, habitual yogurt consumption in infancy was significantly associated with atopic dermatitis (aOR in model 4: ISAAC criteria, 0.69; 95% CI, 0.48–0.99; $P=0.046$; UKWP criteria 0.69; 95% CI, 0.48–0.98; $P=0.038$) and sensitization to foods (aOR, 0.51; 95% CI, 0.27–0.96; $P=0.038$) when the children were 5 years old (Table 2).

Additionally, we evaluated for associations between the frequency of consumption of yogurt in infants and development of atopic dermatitis and sensitization to foods to further investigate the protective effect of habitual yogurt consumption in infancy on atopic dermatitis and sensitization to foods. When the frequencies were classified into “none”, “sometimes” and “every day”, there were significant differences ($p<0.05$) in both groups of yogurt-consuming children compared to the no consumption group (Table 3), and aOR decreased as the exposure frequency increased (P trend <0.05 for each model in Table 3).

4. Discussion

Our study demonstrated a protective effect of habitual yogurt consumption in infancy on atopic dermatitis and food sensitization, but not on other allergic diseases or other sensitizations at 5 years of age.

Our results are in line with previous studies that suggested that use of probiotics in these populations might reduce the risk of atopic dermatitis, whereas there is no proven effect on development of other allergies [15–21]. At present, few studies have examined for associations between habitual yogurt consumption in infancy and development of allergic diseases. Previously, the PASTURE study investigated the relationship between food introduction and atopic dermatitis and found that introduction of yogurt in the first year of life reduced the risk for atopic dermatitis up to 4 years of age [9]. Our results from an urban area of Tokyo supported the findings of the PASTURE study from rural areas in 5 European countries. Furthermore, our data revealed that habitual consumption, i.e., the “every day” group, showed a tendency for lower odds ratios, compared to occasional consumption, i.e., the “sometimes” group. This observation may support the positive association between yogurt consumption during infancy and reduced risk of developing atopic dermatitis and food sensitization.

Consistent with previous probiotics studies, our study found no association between habitual yogurt consumption in infancy and

other allergic diseases, such as wheeze, asthma and rhinitis, at 5 years of age. Interestingly, habitual yogurt consumption in infancy protected only against sensitization to food allergens, but not inhalant allergens in our study. In the last two decades, the use of probiotics for preventing allergies in children has been extensively investigated. However, heterogeneity in the choice of *Lactobacillus* strains is thought to have resulted in conflicting clinical effects, in regard to allergic sensitization [22,23]. Thus, different strains might affect the results of sensitization and/or sensitization pathways, although the strains used to make commercial yogurt products are often not identified. Recently, clinical and experimental observations strongly indicated that epicutaneous exposure to food proteins on damaged skin was a robust risk factor for sensitization to food allergens [24], whereas several routes may be involved in sensitization to inhalant allergens, leading to airway allergies such as asthma and rhinitis. Therefore, the protective effect of yogurt on food sensitization might be, at least in part, a result of prevention of atopic dermatitis. However, reverse causality cannot be excluded in our study, and causal relationships need to be elucidated.

Yogurt contains *Lactobacillus* species, and it is the most representative probiotic food. Probiotics are thought to be potentially useful not only for supplementation of certain microbes, but also for manipulation of intestinal microbial communities, immunomodulation and fortification of the intestinal barrier. Recent evidence has begun to highlight the critical role of gut microbiome diversity in the pathogenesis of allergy in early childhood [25,26]. Indeed, Dang et al. showed significant benefit from using a mixture of probiotic strains compared to single-strain products. Although a mixture of different probiotic strains might be more effective in promoting an ecological barrier than a single strain, the exact in vivo mechanism of action of probiotics in shaping the immune response still needs to be determined and a number of unanswered questions remain [27]. At least 10–15 different single-strain products of *Lactobacilli* were used to make the yogurt products that are commercially available in our study area. Habitual consumption of readily available multiple-strain yogurt products could be a realistic approach for preventing atopic dermatitis even if the efficacy of each strain has not been assessed.

Our study has some potential limitations. Lack of information regarding the amount of yogurt intake might be considered a major weakness of our study. However, since our main findings were similar to those of earlier studies, the amounts of yogurt/probiotics might not correlate closely with their clinical effects. Another limitation was that the study population was selected from urban areas in Japan, suggesting that our findings might not be applicable to other populations.

Conversely, the present study has several strengths. First, the prospective design excluded the possibility of reverse causality bias. Collection of data on yogurt consumption at 12 months of age prevented recall bias. Second, the study used both the standardized outcome measures of the ISAAC questionnaire and the UKWP diagnostic criteria for atopic dermatitis. Finally, our study had a sufficient sample size, and there was a good retention rate having statistical power.

In conclusion, habitual consumption of readily available yogurt products in infancy may prevent development of atopic dermatitis and food sensitization, but not other allergic outcomes. Further translational studies should be performed to clarify the relationship between yogurt and allergic diseases, as well as the role of the microbiome as a mediator.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

This work was funded by a Grant of National Center for Child Health and Development (26-18).

Acknowledgments

We are grateful to the children and parents who participated in the T-CHILD study. We also thank the various staffs for their cooperation and organization of the T-CHILD study. This work was supported by a Grant of National Center for Child Health and Development (26-18).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jdermsci.2017.01.006>.

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1 **Table E1.** Definitions of outcomes and exposures.

<i>Exposures</i>	
Consumption of dietary yogurt	A positive answer at 12 months of age to the question, “Over the past 12 months, how often did your child eat yogurt or other fermented milk products?” There were 3 possible answers: 1] none, 2] sometimes, and 3] every day, with “3) everyday” being a positive answer.
<i>Outcomes of children at 5 years of age</i>	
Ever wheeze	A positive answer at five years old to the question: “Has your child ever had wheezing or whistling in the chest at any time in the past?”
Current wheeze	A positive answer at five years old to the question: “Has your child ever had wheezing or whistling in the past 12 months?”
Ever asthma	A positive answer by the parent, when the child was five years old, to the question: “Have you ever had asthma?”
Current asthma	A positive answer at five years old to the question: “Has your child ever been diagnosed by a doctor as having asthma in the past 12 months?”
Ever rhinitis	A positive answer at five years old to the question: “Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?”
Current rhinitis	A positive answer at five years old to the question: “In the past 12 months, has your child had a problem with sneezing, or a runny or stuffy nose, when he/she DID NOT have a cold or the flu?”
Ever atopic dermatitis	A positive answer at five years old to the question: “Has your child ever had eczema?”
Current atopic dermatitis	A positive answer at five years old to the questions: “Has your child had this 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?”
UKWP diagnostic criteria	A positive answer at five years old to any of the following: Itchy skin in last 12 months, History of involvement of skin creases, History of asthma or hay fever, History of general dry skin, Visible flexural eczema and Onset at age <2 years.
Sensitization	Positive if a specific IgE level of ≥ 0.3 ISAC standardized units (ISU) was detected for at least one allergen.

2 **Table E2.** List of allergen components.

Allergen component	Allergen source common name	Food	Inhalant
Cynd1	Bermuda grass		Cynd1
Phlp1	Timothy		Phlp1
Phlp2	Timothy		Phlp2
Phlp4	Timothy		Phlp4
Phlp5	Timothy		Phlp5
Phlp6	Timothy		Phlp6
Phlp7	Timothy		Phlp7
Phlp11	Timothy		Phlp11
Phlp12	Timothy		Phlp12
Betv1	Birch		Betv1
Betv2	Birch		Betv2
Betv4	Birch		Betv4
Alng1	Alder		Alng1
Cora1.0101	Hazel pollen		Cora1.0101
Cryj1	Japanese cedar		Cryj1
Cupa1	Cypress		Cupa1
Olee1	Olive		Olee1
Olee2	Olive		Olee2
Plaa1	Plane tree		Plaa1
Plaa2	Plane tree		Plaa2
Amba1	Ragweed		Amba1
Artv1	Mugwort		Artv1
Artv3	Mugwort		Artv3
Parj2	Wall pellitory		Parj2
Salk1	Saltwort		Salk1
Mera1	Annual mercury		
Actd1	Kiwi	Actd1	
Actd2	Kiwi	Actd2	
Actd5	Kiwi	Actd5	
Actd8	Kiwi	Actd8	
Apig1	Celery	Apig1	
Dauc1	Carrot	Dauc1	
Mald1	Apple	Mald1	
Prup1	Peach	Prup1	
Prup3	Peach	Prup3	
Anao2	Cashew nut	Anao2	
Arah1	Peanut	Arah1	
Arah2	Peanut	Arah2	
Arah3	Peanut	Arah3	
Arah8	Peanut	Arah8	
Bere1	Brazil nut	Bere1	
Cora1.0401	Hazel nut	Cora1.0401	
Cora8	Hazel nut	Cora8	
Cora9	Hazel nut	Cora9	
Glym4	Soybean	Glym4	
Glym5	Soybean	Glym5	

Glym6	Soybean	Glym6	
Sesi1	Sesame weed	Sesi1	
Tria18	Wheat	Tria18	
TriaGliadin	Wheat	TriaGliadin	
Tria19.0101	Wheat	Tria19.0101	
TriaaA_TI	Wheat	TriaaA_TI	
Hevb1	Latex		
Hevb3	Latex		
Hevb5	Latex		
Hevb6	Latex		
Hevb8	Latex		
Anac2	Bromelin		
Bosd4	Milk	Bosd4	
Bosd5	Milk	Bosd5	
Bosd6	Milk	Bosd6	
Bosd8	Milk	Bosd8	
Bosdlactoferrin	Milk	Bosdlactoferrin	
Gald1	Egg	Gald1	
Gald2	Egg	Gald2	
Gald3	Egg	Gald3	
Gald5	Egg	Gald5	
Cypc1	Carp	Cypc1	
Gadc1	Cod	Gadc1	
Derf1	House dust mite		Derf1
Derf2	House dust mite		Derf2
Derp1	House dust mite		Derp1
Derp2	House dust mite		Derp2
Derp10	House dust mite		Derp10
Eurm2	Storage mite		Eurm2
Canf1	Dog		Canf1
Canf2	Dog		Canf2
Canf3	Dog		Canf3
Feld1	Cat		Feld1
Feld2	Cat		Feld2
Feld4	Cat		Feld4
Equc3	Horse		Equc3
Musm1	Mouse		Musm1
Alta1	Alternaria		Alta1
Alta6	Alternaria		Alta6
Aspf1	Aspergillus		Aspf1
Aspf2	Aspergillus		Aspf2
Aspf3	Aspergillus		Aspf3
Aspf4	Aspergillus		Aspf4
Aspf6	Aspergillus		Aspf6
Clah8	Cladosporium		Clah8
Apim1	Honey bee venom		
Apim4	Honey bee venom		
Blag1	Cockroach		Blag1

Blag2	Cockroach	Blag2
Blag4	Cockroach	Blag4
Blag5	Cockroach	Blag5
Blag7	Cockroach	Blag7
Anis1	Anisakis	
Anis3	Anisakis	
Pena1	Shrimp	Pena1
Peni1	Shrimp	Peni1
Penm1	Shrimp	Penm1

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48 **Table E3.** Comparison of the characteristics of children by follow-up status.

		Response at 5 years		Lost to follow-up		p
		n	%	n	%	
Habitual yogurt consumption in infancy	no	704	62.0	133	67.5	0.14
	yes	432	38.0	64	32.5	
Parental history of allergic diseases	no	251	22.6	80	25.2	0.325
	yes	860	77.4	237	74.8	
Gender	boy	590	50.6	197	58.3	0.01
	girl	576	49.4	141	41.7	
Preterm birth	>=37 weeks	1082	92.8	312	92.3	0.76
	<37 weeks	84	7.2	26	7.7	
Season of birth	spring-summer	565	48.5	186	55.0	0.034
	fall-winter	600	51.5	152	45.0	
Smoking during pregnancy	no	1139	98.0	321	95.3	0.01
	yes	23	2.0	16	4.7	
Pet ownership	no	320	27.4	91	26.9	0.85
	yes	846	72.6	247	73.1	
Breast feeding	0-5 months	172	15.1	46	23.4	0.004
	>=6 months	966	84.9	151	76.6	
Timing of solid food introduction	<6 months	525	46.2	88	44.9	0.74
	>=6 months	612	53.8	108	55.1	
History of food allergy at 1 year	no	1017	90.8	176	92.1	0.55
	yes	103	9.2	15	7.9	
History of eczema until 1year	no	254	22.3	56	28.4	0.06
	yes	884	77.7	141	71.6	
History of wheeze at 1 year	no	909	80.1	145	73.6	0.04
	yes	226	19.9	52	26.4	
Number of previous live births	0	674	57.9	136	40.2	<0.001
	>=1	491	42.1	202	59.8	
Daycare during infancy	no	903	79.6	157	80.1	0.86
	yes	232	20.4	39	19.9	
Cesarean section	no	887	76.3	255	75.7	0.8
	yes	275	23.7	82	24.3	

* After data selection, 1504 cases remained and comprised the baseline cohort, which included singletons and one child from each multiple birth. 1,166 children's parents responded to the questionnaire at 5 years of age.

Table E4. Comparison of the characteristics of children by habitual yogurt consumption in infancy.

		No		Yes		P
		n	%	n	%	
Parental history of allergic diseases	no	146	21.7	98	23.9	0.40
	yes	527	78.3	312	76.1	
	missing	53				
Gender	boy	353	50.1	223	51.6	0.63
	girl	351	49.9	209	48.4	
Preterm birth	≥37 weeks	658	93.5	399	92.4	0.48
	<37 weeks	46	6.5	33	7.6	
Season of birth	spring-summer	338	48.0	214	49.7	0.59
	fall-winter	366	52.0	217	50.3	
	missing	1				
Smoking during pregnancy	no	688	97.9	421	98.1	0.76
	yes	15	2.1	8	1.9	
	missing	4				
Pet ownership	no	194	27.6	114	26.4	0.67
	yes	510	72.4	318	73.6	
Breast feeding	0-5 months	102	14.5	69	16.0	0.50
	≥6 months	602	85.5	363	84.0	
Timing of solid food introduction	<6 months	318	45.2	207	47.9	0.37
	≥6 months	386	54.8	225	52.1	
History of food allergy at 1 year	no	631	90.7	385	91.2	0.75
	yes	65	9.3	37	8.8	
	missing	18				
History of eczema until 1 year	no	160	22.7	94	21.8	0.70
	yes	544	77.3	338	78.2	
History of wheeze at 1 year	no	547	78.0	360	83.3	0.08
	yes	154	22.0	72	16.7	
	missing	3				
Number of previous live births	0	364	51.7	296	68.7	<0.001
	≥1	340	48.3	135	31.3	
	missing	1				
Daycare during infancy	no	548	78.0	354	82.3	0.03
	yes	155	22.0	76	17.7	
	missing	3				
Cesarean section	no	539	76.8	329	76.5	0.92
	yes	163	23.2	101	23.5	
	missing	4				

N=1,136, including those whose parents responded at 12 months to the question regarding habitual yogurt consumption in infancy and responded to the questionnaire at 5 years of age.