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Original Article

Breastfeeding and risk of food allergy: A nationwide birth cohort in Japan

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ABSTRACT

Background: Although breastfeeding has been well-established as the preferred method for infant nutrition, its prophylactic effects on food allergy remain controversial. Infantile eczema has been linked to food allergy via percutaneous sensitization; however, this relationship has not been considered in previous studies. We aimed to uncover the prophylactic effects of breastfeeding on food allergy, focusing on eczema-mediated percutaneous sensitization.

Methods: This retrospective cohort study was based on 46,616 children from the Longitudinal Survey of Newborns in the 21st Century in Japan, begun in 2001. We classified participants into three groups based on infant feeding practices (exclusive breastfeeding, partial breastfeeding including only colostrum, and formula feeding only) and used information from at least one outpatient visit for food allergy during two observation periods (age 6–18 months and age 6–66 months) as health outcomes. We performed log-binomial regression analysis adjusted for potential confounders and stratified analysis according to infantile eczema status.

Results: Compared with formula feeding, partial breastfeeding including only colostrum reduced the risk of food allergy only in children with infantile eczema, (RR = 0.66, 95% CI: 0.46, 0.96 for age 6–66 months), whereas exclusive breastfeeding increased this risk in those without infantile eczema (RR = 2.41, 95% CI: 1.40, 4.15, age 6–66 months). The prophylactic effects of breastfeeding on food allergy in the infantile eczema group increased with shorter breastfeeding duration.

Conclusions: Our results showed that breastfeeding, especially colostrum, had prophylactic effects on food allergy only among high-risk children with infantile eczema whereas prolonged breastfeeding increased the risk of food allergy.

Introduction

Breastfeeding has been the preferred method for infant nutrition, and the accumulated evidence indicates that breastfeeding can decrease the risk of morbidity such as infectious diseases, overweight/obesity, and diabetes; breastfeeding may also increase intellectual ability among children.[1] Because breast milk contains many active immune factors such as cytokines, inflammatory mediators, signaling molecules, and soluble receptors,[2] it may also reduce the risk of allergic diseases such as food allergy; however, there have been conflicting findings in this regard.[3,4] Indeed, a recent meta-analysis showed no statistically significant association between breastfeeding and food allergy.[5] Large variations in active immune factors such as cytokines, inflammatory mediators, signaling molecules the concentrations of immunomodulatory components in breast milk, as well as personal traits, may complicate study results.[6] An important reason for such inconsistencies could be that previous studies have not considered individual risk factors, such as infantile eczema, which may have an important role in triggering food allergy, most likely via percutaneous sensitization.

Percutaneous sensitization is a recently recognized theory, together with a dual-allergen exposure hypothesis, that oral intake of food proteins promotes immune tolerance whereas percutaneous exposure tends to induce allergic sensitization.[7] Indeed,

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recent epidemiological and experimental studies strongly suggest that percutaneous (i.e., “eczema”tous) sensitization is a risk factor for allergic diseases, including food allergy.[8] However, little has been reported on the association between breastfeeding and food allergy, with a focus on percutaneous sensitization risk.

Therefore, in the present study, we used data from a large nationwide birth cohort in Japan to investigate whether breastfeeding is associated with the risk of food allergy in the presence or absence of infantile eczema, which is linked to percutaneous (i.e., per“eczema”tous) sensitization.

Methods

Participants

This was a nationwide retrospective cohort study. The Japanese Ministry of Health, Labor and Welfare has conducted “The Longitudinal Survey of Babies in the Twenty-first Century” since 2001, to investigate measures that can be taken to counter the declining birthrate in Japan.[9–11] The survey targeted all babies born in Japan between 10 and 17 January or 10 and 17 July in 2001. Baseline questionnaires were mailed to a total of 53,575 families when eligible babies were 6 months old. Of these, 47,017 families initially completed the baseline questionnaires (88% response rate); these respondents are sent follow-up questionnaires annually. Birth record data from vital statistics of Japan are also linked with each targeted child.

Because we investigated the role of breastfeeding in food allergy among preschool-age children in the present study, we obtained data from the first to the sixth survey (child's age 6 months–66 months). We excluded 401 children with missing information on infant feeding practices obtained at the first survey, leaving 46,616 children included in the analysis (Supplementary Fig. 1).

Infant feeding practices

The information on infant feeding practices was collected at the first survey (child's age 6 or 7 months). Participants responded to questions about breastfeeding (infant was breastfed, only fed colostrum, or never breastfed) and formula feeding (infant was fed formula or never fed formula). We then formed three categories as the main exposures of interest, as follows: formula feeding only (never breastfed), partial breastfeeding including only colostrum, and exclusive breastfeeding.

Food allergy

The second to sixth surveys queried whether the child had attended an outpatient clinic for various common diseases such as food allergy. Respondents marked up the assigned number of food allergy in the questionnaire when their children had attended an outpatient clinic for food allergy at least once in the previous 12 months. To investigate the associations between breastfeeding and food allergy during the infantile and preschool periods, we set two observation periods: from age 6–18 months and from age 6–66 months. We then used information from at least once outpatient visit for food allergy during the two observation periods as the outcome of interest.

Infantile eczema including atopic dermatitis

We obtained the information on infantile eczema from the second survey (child's age 18 months). In the questionnaire, respondents marked up the assigned number of eczema including atopic dermatitis when their children had attended an outpatient clinic for eczema or atopic dermatitis at least once in the previous 12 months.

Statistical analysis

We first compared baseline characteristics among the three infant feeding practice groups (formula feeding only, partial breastfeeding including only colostrum, and exclusive breastfeeding). To evaluate potential selection bias as a result of loss to follow-up, we also compared baseline characteristics between children included in the analysis and children lost to follow-up through the sixth survey (i.e., 66 months of age).

We then conducted a log-binomial regression analysis to investigate the association between infant feeding practices and children's outpatient visits for food allergy. We estimated adjusted risk ratios (RRs) and their 95% confidence intervals (CIs), controlling for potential confounders using the formula feeding group as reference.

We selected the following biological and socioeconomic factors as potential confounding factors. Biological factors included sex (dichotomous), parity including delivery of the child (1, 2, $\geq$3; categorical), singleton or multiple birth (dichotomous), term or preterm birth (<37 weeks of gestation; dichotomous), normal or low birth weight (<2500 g; dichotomous) and maternal age at delivery (<25, 25–29, 30–34, and $\geq$35 years; categorical). The information on parity included the presence or absence of older siblings. Socioeconomic factors included maternal educational attainment (university or higher, junior college, high school, junior high school, or other; categorical), smoking status (non-smoker, smokes <10 cigarettes per day, and smokes $\geq$10 cigarettes per day; categorical), place of birth and residence (ward, city, town, or village; categorical), and daycare attendance at 18 months old (dichotomous). We retrieved the data on birth weight, sex, parity, maternal and paternal age at delivery, and place of birth and residence from birth records. The information on maternal smoking status was obtained in the first survey, and information on maternal educational attainment and daycare attendance were obtained in the second survey. These potential confounders were selected based on earlier studies or prior knowledge of the association between breastfeeding and allergic diseases.[1] Cases with missing data were excluded and we conducted our analysis with complete cases only.

To examine the impact of breastfeeding on food allergy in greater detail, we further classified the “partial breastfeeding including only colostrum” infant feeding practice group, using the information on breastfeeding duration obtained in the first survey; we then created the following category for feeding practices: formula feeding without colostrum (never breastfed), formula feeding with colostrum, partial breastfeeding for 1–2 months, for 3–5 months, for 6–7 months, and exclusive breastfeeding for longer than 6–7 months. We then repeated the analysis using formula feeding without colostrum group as reference.

As described, recent findings strongly suggest that per“-eczema”tous sensitization drives atopic march. Therefore, we additionally conducted stratified analyses according to whether children had attended an outpatient clinic for eczema, including atopic dermatitis, during the weaning period (age 6–18 months). We also conducted a test of interaction by entering into the model multiplicative terms between eczema and dichotomized breastfeeding status. For the interaction test, we combined the latter two categories of the original infant feeding practices (i.e., partial breastfeeding including only colostrum, and exclusive breastfeeding) to obtain the dichotomized breastfeeding status (formula feeding only vs. any breastfeeding including only colostrum).

The statistical analyses were performed using Stata version 13 (StataCorp LLC, College Station, TX, USA). P values less than 0.05 were considered significant. This study was approved by the Institutional Review Board at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No.1506-073)

Results

Participants' demographic characteristics, according to infant feeding practices, are shown in Table 1. Breastfed children tended to have more siblings ($p < 0.001$), mothers with higher academic attainment ($p < 0.001$), and non-smoking mothers ($p < 0.001$) than formula-fed children. Additionally, breastfed children were less likely to be associated with low birthweight ($p < 0.001$) and preterm birth ($p < 0.001$) and less likely to attend childcare centers ($p < 0.001$) than formula-fed children. During follow-up, 3035 children were lost to follow-up at the second survey (i.e., 18 months of age) and 11,069 children were lost to follow-up by the sixth survey (i.e., 66 months of age). Children lost to follow-up tended to be less exclusively breastfed ($p < 0.001$) and to have younger mothers ($p < 0.001$), mothers who smoked ($p < 0.001$), and mothers with lower academic attainment ($p < 0.001$) than children included in the analysis (Table 2).

We calculated the RRs of food allergy in all participants and according to eczema status during the weaning period (Table 3). Children with eczema had higher incidence of food allergy compared with those who did not have eczema, e.g., 14.2% in children with eczema and 2.8% in those without eczema during the period of age 6–18 months ($p < 0.001$). As shown in Table 3, exclusive breastfeeding increased the risk of food allergy in both the observation periods, compared with formula feeding only ($p = 0.04$ for age 6–18 months and $p = 0.02$ for age 6–66 months). When we stratified the participants according to infantile eczema status, exclusive breastfeeding again increased the risk of food allergy in the group without infantile eczema ($p = 0.01$ for age 6–18 months and $p < 0.001$ for age 6–66 months) whereas partial breastfeeding lowered the risk of food allergy in the group with infantile eczema. In the infantile eczema group, the observed RRs for partial breastfeeding including only colostrum were 0.63 (95% CI, 0.41–0.96) for children aged 6–18 months and 0.66 (95% CI, 0.46–0.96) for those aged 6–66 months.

Table 1
Demographic characteristics of children included in the analysis at age 18 months, by infant feeding practice (N = 46,616).

	Formula feeding only (n = 795)	Partial breastfeeding (n = 36,020)	Exclusive breastfeeding at 6–7 months of age (n = 9801)	P value†
Gender, n (%)				0.01*
Boys	437 (55.0)	18,804 (52.2)	4979 (50.8)	
Girls	358 (45.0)	17,216 (47.8)	4822 (49.2)	
Birth weight, n (%)				<0.001*
<2500 g	121 (15.2)	3398 (9.4)	453 (4.6)	
≥2500 g	674 (84.8)	32,622 (90.6)	9348 (95.4)	
Term or preterm birth, n (%)				<0.001*
Term	710 (89.3)	33,991 (94.4)	9551 (97.5)	
Preterm	85 (10.7)	2029 (5.6)	250 (2.5)	
Singleton or multiple birth, n (%)				<0.001*
Singleton birth	772 (97.1)	35,080 (97.4)	9788 (97.4)	
Multiple birth	23 (2.9)	940 (2.6)	940 (2.6)	
Parity, n (%)				<0.001*
1 (no older siblings)	371 (46.7)	18,447 (51.2)	3982 (40.6)	
2	264 (33.2)	12,556 (34.9)	4125 (42.1)	
≥3	160 (20.1)	5007 (13.9)	1694 (13.9)	
Daycare attendance, n (%)				<0.001*
No	597 (75.1)	27,779 (77.1)	8043 (82.1)	
Yes	97 (12.2)	5676 (15.8)	1323 (13.5)	
Missing	101 (12.7)	2565 (7.1)	435 (4.4)	
Maternal age at delivery, n (%)				<0.001*
<25	103 (13.0)	4981 (13.8)	1011 (10.3)	
25–30	261 (32.8)	13,658 (37.9)	3770 (38.5)	
30–35	260 (32.7)	12,549 (34.8)	3815 (38.9)	
≥35	171 (21.5)	4832 (13.4)	1205 (12.3)	
Maternal smoking status, n (%)				<0.001*
No	551 (69.3)	28,784 (79.9)	8926 (91.1)	
Yes <10/day	117 (14.7)	4419 (12.3)	620 (6.3)	
Yes ≥10/day	107 (13.5)	2573 (7.1)	211 (2.2)	
Missing	20 (2.5)	244 (0.7)	44 (0.5)	
Maternal educational attainment, n (%)				<0.001*
University or higher	41 (5.2)	4321 (12.0)	1641 (16.7)	
Junior college	200 (25.2)	13,500 (37.5)	4216 (43.0)	
High school	355 (44.7)	13,508 (37.5)	3139 (32.0)	
Junior high school or others	92 (11.6)	2002 (5.6)	322 (3.3)	
Missing	107 (13.5)	2689 (7.5)	483 (4.9)	
Residential area, n (%)				0.004*
Wards	156 (19.6)	2232 (22.8)	7834 (21.8)	
Cities	452 (56.9)	5709 (58.3)	21,314 (59.2)	
Towns or villages	187 (23.5)	1860 (19.0)	8919 (19.1)	
Eczema at 6–18 months old				<0.001*
No	599 (85.8)	28,039 (83.7)	7665 (81.8)	
Yes	99 (14.2)	5468 (16.3)	1711 (18.3)	

*$p < 0.05$.
† P values were calculated by chi-square test to examine the difference between three infant feeding practice categories.

Table 2
Baseline characteristics of eligible children with and without outpatient visit data (N = 46,616).

	Eligible children	Children analyzed at age 18mo	Children loss to follow-up at 18mo	P value†	Children analyzed at age 66mo	Children loss to follow-up at 66mo	P value†
	(n = 46,616)	(n = 43,581)	(n = 3035)		(n = 35,547)	(n = 11,069)	
Infant feeding practice, n (%)				<0.001*			<0.001*
Formula feeding only	795 (1.7)	698 (1.6)	97 (3.2)		471 (1.4)	324 (2.5)	
Partial breastfeeding	36,020 (75.6)	33,507 (76.9)	2513 (82.8)		25,526 (76.2)	10,494 (80.0)	
Exclusive breastfeeding to 6–7M	9801 (22.7)	9376 (21.5)	425 (14.0)		7500 (22.4)	2301 (17.5)	
Gender, n (%)				0.97			0.6
Boys	24,220 (52.0)	22,644 (52.0)	1576 (51.9)		18,444 (51.9)	5776 (52.2)	
Girls	22,396 (48.0)	20,937 (48.0)	1459 (48.1)		17,103 (48.1)	5293 (47.8)	
Birth weight, n (%)				<0.001*			<0.001*
<2500 g	3972 (8.5)	3669 (8.4)	303 (10.0)		2945 (8.3)	1027 (9.3)	
≥2500	42,644 (91.5)	39,912 (91.6)	2732 (90.0)		32,602 (91.7)	10,042 (90.7)	
Term or preterm birth, n (%)				<0.001*			<0.001*
Term birth	44,252 (94.9)	41,418 (95.0)	2834 (93.4)		33,834 (95.2)	10,418 (94.2)	
Preterm birth	2364 (5.1)	2163 (5.0)	201 (6.6)		1713 (4.8)	651 (5.9)	
Singleton or multiple birth, n (%)				0.01*			<0.001*
Singleton birth	45,640 (97.9)	42,689 (97.9)	2951 (97.2)		34,842 (98.0)	10,798 (97.6)	
Multiple birth	976 (2.1)	892 (2.1)	84 (2.8)		705 (2.0)	271 (2.5)	
Parity, n (%)				0.04*			<0.001*
1 (no older siblings)	22,800 (48.9)	21,319 (48.9)	1481 (48.8)		17,359 (48.8)	5441 (49.2)	
2	16,955 (36.4)	15,892 (36.5)	1063 (35.0)		13,085 (36.8)	3870 (35.0)	
≥3	6861 (14.7)	6370 (14.6)	491 (16.2)		5103 (14.4)	1758 (15.9)	
Daycare attendance at 18 mo							<0.001*
No	36,419 (78.1)	36,419 (83.6)	NA		29,905 (84.1)	6514 (58.9)	
Yes	7096 (15.2)	7096 (16.3)	NA		5595 (15.7)	1501 (13.6)	
Missing	3101 (6.7)	66 (0.2)	3035 (100.0)		47 (0.1)	3054 (27.6)	
Maternal age at delivery, n (%)				<0.001*			<0.001*
<25	6095 (13.1)	5249 (12.0)	846 (27.9)		3536 (10.0)	2559 (23.1)	
25–30	17,689 (38.0)	16,570 (38.0)	1119 (36.9)		13,504 (38.0)	4185 (37.8)	
30–35	16,624 (35.7)	15,845 (36.4)	779 (25.7)		13,431 (37.8)	3193 (28.9)	
≥35	6208 (13.3)	5917 (13.6)	291 (9.6)		5076 (14.3)	1132 (10.2)	
Maternal smoking status, n (%)				<0.001*			<0.001*
No	38,261 (82.1)	36,304 (83.3)	1957 (64.5)		30,522 (85.9)	7739 (69.9)	
Yes <10/day	5156 (11.1)	4607 (10.6)	549 (18.1)		3275 (9.2)	1881 (17.0)	
Yes ≥10/day	2891 (6.2)	2402 (5.5)	489 (16.1)		1565 (4.4)	1326 (12.0)	
Missing	308 (7.0)	268 (0.6)	40 (1.3)		185 (0.5)	123 (1.1)	
Maternal educational attainment, n (%)							<0.001*
University or higher	2416 (5.2)	2416 (5.5)	NA		5285 (14.9)	718 (6.5)	
Junior college	17,002 (36.5)	17,002 (39.0)	NA		15,166 (42.7)	2750 (24.8)	
High school	17,916 (38.4)	17,916 (41.1)	NA		13,396 (37.7)	3606 (32.6)	
Junior high school or others	6003 (12.9)	6003 (13.8)	NA		1520 (4.3)	896 (8.1)	
Missing	3279 (7.0)	244 (0.6)	3035 (100.0)		180 (0.5)	3099 (28.0)	
Residential area, n (%)				0.24			0.37
Wards	10,222 (21.9)	9582 (22.0)	640 (21.1)		7839 (22.1)	2383 (21.5)	
Cities	27,475 (58.9)	25,692 (59.0)	1783 (58.7)		20,946 (58.9)	6529 (59.0)	
Towns or villages	8919 (19.1)	8307 (19.0)	612 (20.2)		6762 (19.0)	2157 (19.5)	
Eczema at 6–18 months old							<0.001*
No	36,303 (83.3)	36,303 (83.3)	NA		29,498 (83.0)	6805 (84.7)	
Yes	99 (14.2)	99 (14.2)	NA		6049 (17.0)	1229 (15.3)	

mo, months; NA, not applicable.
*p < 0.05.
† P values were calculated by chi-square test to examine the difference between children included in the analysis and children lost to follow-up.

When we examined the impact of breastfeeding more in detail, breastfeeding increased the risk of food allergy as breastfeeding duration became longer regardless of whether infantile eczema exists. By contrast, the prophylactic effects of breastfeeding were stronger as breastfeeding duration became shorter and colostrum seemed to play an important role on preventing food allergy in the infantile eczema group (Table 4). For example, compared with formula feeding only, formula feeding with colostrum significantly decreased the risk of food allergy among children with infantile eczema in both the observation periods (RR, 0.44; 95% CI, 0.25–0.78, p = 0.01 for age 6–18 months and RR, 0.57; 95% CI, 0.36–0.91, p = 0.02 for age 6–66 months). This was supported by the interaction test (Fig. 1), and the RRs for dichotomized breastfeeding status (formula feeding only vs. partial or exclusive breastfeeding including only colostrum) were significantly different between children with eczema and those without eczema, i.e., p-values for interaction were 0.012 for age 6–18 months and 0.007 for age 6–66 month.

Discussion

In the present study, we investigated whether breastfeeding was associated with the risk of food allergy in the presence or absence of infantile eczema, which is linked to percutaneous sensitization. In the entire group, exclusive breastfeeding increased the risk of food allergy. However, in the stratified analysis according to infantile eczema status, although breastfeeding increased the risk of food allergy in the group without infantile eczema, it lowered the risk of food allergy in the group with infantile eczema. Moreover, the prophylactic effects of

Table 3
Breastfeeding and outpatient visits for food allergy from age 6–18 months and 6–66 months.

	Total			without Eczema			with Eczema		
	case/N (%)	RR (95%CI)	P value	case/N (%)	RR (95%CI)	P value	case/N (%)	RR (95%CI)	P value
Between 6 and 18 months									
Formula feeding without colostrum	25/698 (3.6)	1		7/599 (1.2)	1		18/99 (18.2)	1	
Partial breastfeeding	1427/33,507 (4.3)	1.04 (0.71–1.54)	0.83	720/28,039 (2.6)	1.97 (0.94–4.13)	0.07	707/5468 (12.9)	0.63 (0.41–0.96)	0.03*
Exclusive breastfeeding	588/9376 (6.3)	1.52 (1.02–2.25)	0.04*	279/7665 (3.6)	2.87 (1.36–6.06)	0.01*	309/1711 (18.1)	0.85 (0.55–1.30)	0.45
Between 6 and 66 months									
Formula feeding without colostrum	37/522 (7.1)	1		13/442 (2.9)	1		21/77 (27.3)	1	
Partial breastfeeding	2254/27,561 (8.2)	1.15 (0.83–1.59)	0.42	1287/22,853 (5.6)	1.83 (1.07–3.14)	0.03*	933/4674 (20.0)	0.66 (0.46–0.96)	0.03*
Exclusive breastfeeding	832/8019 (10.4)	1.50 (1.08–2.10)	0.02*	446/6500 (6.9)	2.41 (1.40–4.15)	<0.001*	375/1508 (24.9)	0.81 (0.56–1.18)	0.28

N, number of children; RR, risk ratio; CI, confidence interval.
Adjusted for sex, parity, singleton or multiple birth, term or preterm birth, normal or low birth weight, maternal age at delivery, maternal educational attainment, maternal smoking status, place of birth and residence, and daycare attendance.
*$p < 0.05$.

Table 4
Breastfeeding duration and outpatient visits for food allergy from age 6–18 months and 6–66 months.

	Total			without Eczema			with Eczema		
	case/N (%)	RR (95%CI)	P value	case/N (%)	RR (95%CI)	P value	case/N (%)	RR (95%CI)	P value
Between 6 and 18 months									
Formula feeding without colostrum	25/698 (3.6)	1		7/599 (1.2)	1		18/99 (18.2)	1	
Partial breastfeeding (duration, mo)									
Only colostrum	59/1946 (3.0)	0.78 (0.49–1.24)	0.3	34/1657 (2.1)	1.63 (0.73–3.67)	0.24	25/289 (8.7)	0.44 (0.25–0.78)	0.01*
1–2	254/8486 (3.0)	0.78 (0.52–1.17)	0.23	133/7237 (1.8)	1.48 (0.69–3.14)	0.31	121/1249 (9.7)	0.50 (0.32–0.79)	<0.001*
3–5	364/8545 (4.3)	1.06 (0.71–1.58)	0.77	189/7204 (2.6)	2.05 (0.97–4.34)	0.06	175/1341 (13.1)	0.64 (0.41–1.00)	0.048*
6–7	732/14,199 (5.2)	1.23 (0.83–1.82)	0.3	355/11,661 (3.0)	2.31 (1.10–4.86)	0.03*	377/2538 (14.9)	0.71 (0.47–1.10)	0.12
Exclusive breastfeeding to 6–7mo of age	588/9376 (6.3)	1.55 (1.05–2.30)	0.03*	279/7665 (3.6)	2.95 (1.40–6.22)	<0.001*	309/1711 (18.1)	0.87 (0.56–1.33)	0.51
P for trend		<0.001*			<0.001*			<0.001*	
Between 6 and 66 months									
Formula feeding without colostrum	37/522 (7.1)	1		13/442 (2.9)	1		21/77 (27.3)	1	
Partial breastfeeding (duration, mo)									
Only colostrum	106/1513 (7.0)	0.94 (0.65–1.38)	0.77	62/1276 (4.9)	1.54 (0.85–2.77)	0.15	39/232 (16.8)	0.57 (0.36–0.91)	0.02*
1–2	456/6618 (6.9)	0.97 (0.69–1.35)	0.85	272/5589 (4.9)	1.55 (0.90–2.69)	0.11	174/1019 (17.1)	0.59 (0.40–0.86)	0.01*
3–5	596/7006 (8.5)	1.19 (0.85–1.66)	0.3	351/5851 (6.0)	1.97 (1.14–3.40)	0.02*	229/1139 (20.1)	0.67 (0.46–0.98)	0.04*
6–7	1070/12,155 (8.8)	1.26 (0.90–1.75)	0.18	588/9907 (5.9)	1.99 (1.16–3.42)	0.01*	479/2245 (21.3)	0.71 (0.49–1.02)	0.07
Exclusive breastfeeding to 6–7mo of age	832/8019 (10.4)	1.53 (1.10–2.13)	0.01*	446/6500 (6.9)	2.45 (1.42–4.22)	<0.001*	375/1508 (24.9)	0.82 (0.57–1.20)	0.31
P for trend		<0.001*			<0.001*			<0.001*	

N, number of children; mo, months; RR, risk ratio; CI, confidence interval.
Adjusted for sex, parity, singleton or multiple birth, term or preterm birth, normal or low birth weight, maternal age at delivery, maternal educational attainment, maternal smoking status, place of birth and residence, and daycare attendance.
*$p < 0.05$.

breastfeeding among children with infantile eczema became stronger with shorter breastfeeding duration, and colostrum feeding seemed to play an important role.

Because no prior attempts have been made to evaluate the association between breastfeeding and food allergy by focusing on per“eczema”tous sensitization, our study findings cannot be compared with those of previous studies. For example, Luccioli *et al.* reported that exclusive breastfeeding for more than 4 months had a preventive effect on food allergy among low-risk children, defined according to family history of allergic diseases and eczema before 1 year of age.[4] However, the sample size of that previous study was small (n = 1363), which hampered the interpretation of the study findings.

The prophylactic role of breastfeeding or colostrum on the risk of food allergy in the presence of eczema could be explained by the dual allergen exposure hypothesis. According to this hypothesis, the occurrence of food allergy is related to the balance between skin percutaneous sensitization and oral tolerance.[7] Children with infantile eczema who lose this balance because of strong skin barrier dysfunction may receive benefit from breastfeeding, to maintain appropriate oral tolerance that can prevent the development of food allergy. Indeed, mother's breast milk, particularly colostrum, contains many immune factors such as immunoglobulin A, that can affect the development and maintenance of intestinal immune regulation related to oral tolerance.[12] Moreover, the risk of skin percutaneous sensitization may also be altered by breast milk. Although it is not clear why breast milk, particularly colostrum, reduced the risk of food allergy only among children with infantile eczema, breast milk and its constituents (e.g., immune factors in colostrum) may affect the risk of percutaneous sensitization only among children with infantile eczema. For example, Bottcher *et al.* reported that low transforming growth factor-β2 in breast milk induced by Lactobacillus reuteri supplementation is associated with reduced risk of sensitization during infancy.[13] These complex mechanisms may partly explain the observed finding, but further studies are warranted to elucidate this.

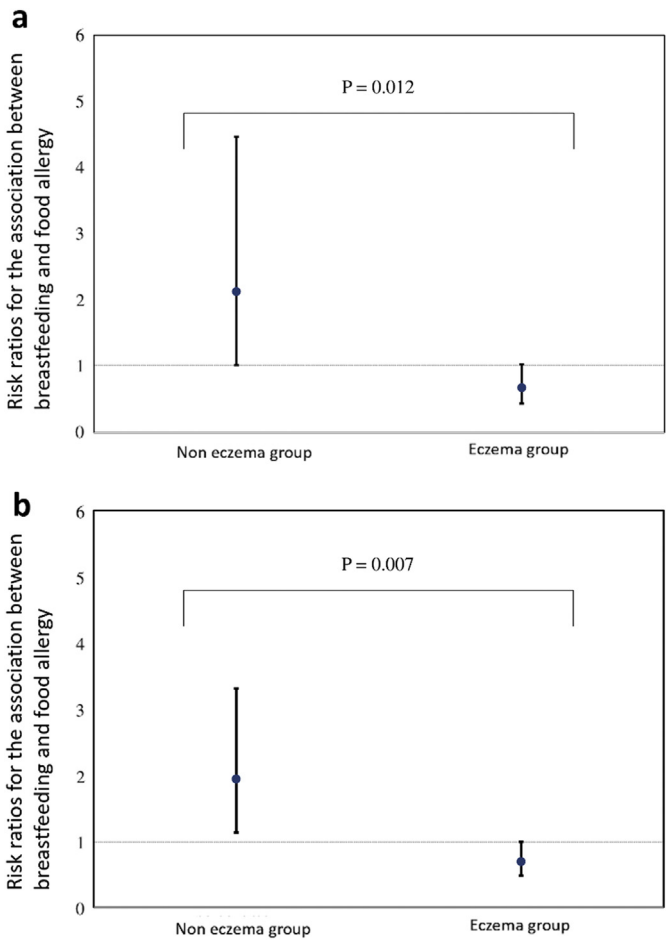

Fig. 1. Risk ratios for the association between dichotomized breastfeeding status (formula feeding only vs. any breastfeeding including only colostrum) and outpatient visits for food allergy stratified by eczema status during ages 6–18 months **(a)** and ages 6–66 months **(b)**. The category of "formula feeding only" was used as reference. The p-values from a test of multiplicative interaction are provided.

By contrast, exclusive or prolonged breastfeeding increased the risk of food allergy among children without eczema and exclusive or prolonged breastfeeding attenuated the prophylactic effect of breastfeeding, even among some children with eczema. This could be explained by the ingredients in mature milk or behavioral patterns, such as delayed food introduction caused by exclusive or prolonged breastfeeding. For example, Onizawa *et al.* reported that early introduction of cow's milk formula was associated with lower incidence of IgE-mediated cow's milk allergy.[14] Therefore, exclusive or prolonged breastfeeding can prevent the early intake of cow's milk protein and increase the risk of cow's milk allergy. Since we do not have information on when each participant introduced solid food, we cannot discuss about whether prolonged breastfeeding itself or delayed food introduction affected the risk of food allergy in the present study. Moreover, prolonged breastfeeding seemed to attenuate the beneficial effects of colostrum on food allergy among the participants with infantile eczema, implicating possible differential roles between colostrum and mature milk. Further studies will be needed on this issue. But, it is noteworthy that the prevalence of food allergy was much higher among children with eczema compared with those who did not have eczema (Table 3); therefore, the positive impact of breastfeeding, especially colostrum, against food allergy in children with infantile eczema could outweigh the negative impact in those without infantile eczema, in terms of public health.

The strength of the present study was that we included participants from a large nationwide population-based study. In addition, we adjusted extensively for possible biological and socioeconomic confounders. However, our study also has some limitations. First, although we adjusted possible confounders, there was no information about familial history of allergic diseases. Individual genetic predisposition, such as a defect in the filaggrin gene, could be responsible for the development of chronic eczema, such as atopic dermatitis,[15] and genetic predisposition can best be assessed using information of family history.[16] Future studies should be performed that include family history information, to clinically recommend breastfeeding or colostrum in high-risk infants. Second, the information on food allergy was obtained from parental reports not from clinically confirmed methods. However, this possible misclassification would be nondifferential, moving the effect estimates toward the null. Third, the information on breastfeeding was also obtained from parental reports. However, this information was collected at 6 months of age, prior to the collection of information on disease status. Thus, this possible misclassification would not cause bias. Fourth, infantile eczema status queried at the second survey included an outpatient clinic attendance either due to infantile eczema or atopic dermatitis. Infantile eczema is generally regarded as dry skin, itchy rashes for two weeks or more in typical location, whereas atopic dermatitis is chronic eczema caused by atopic conditions. They are both associated with skin barrier dysfunction and risk of per"eczema"tous sensitization. Moreover, Ballardini *et al.* indicated the infantile eczema itself is associated with increased risk of allergy-related diseases in preadolescence.[17] Therefore, the stratified analysis by the infantile eczema status queried at the second survey would be acceptable. Finally, some participants were lost to follow-up, particularly by time of the sixth survey (i.e., 66 months of age), which can cause selection bias. However, the results obtained did not differ substantially between study periods (i.e., between age 6–18 months and age 6–66 months), so this selection bias would not be large. Finally, we targeted Japanese children, which might prevent generalizability of the findings to other populations.

In conclusion, our study showed that infantile eczema status modified the associations between breastfeeding and food allergy. Prolonged breastfeeding increased the risk of food allergy, whereas breastfeeding, especially colostrum, had prophylactic effects on food allergy among high-risk children with infantile eczema. Further studies on the role of breastmilk will provide new insights into the prevention and treatment of food allergy in children.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2019.08.007.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

NM designed the study, and wrote the initial draft of the manuscript. TY contributed to data collection, interpretation of data, and assisted in the preparation of the manuscript.

KN, MI, HT and HD contributed to interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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