

RESEARCH LETTER

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Associations of frequent emollient use with wheeze and asthma in young Japanese children: A survey of well-child visits

Allergic diseases are a disorder of the immune system characterized by complex networks among multiple organs. Young children have shown variations of allergic symptoms. Previously, we reported the complex relationships among serum multiple cytokines/chemokines and allergic signs and symptoms of atopic dermatitis and asthma in a birth cohort using the artificial intelligence (AI) technique.¹ Damaged skin and respiratory and gut mucosal barriers are vulnerable to various external threats such as allergens, infections and environmental exposures.² Akdis proposed the epithelial barrier hypothesis, which suggests that the impaired skin barrier is linked to atopic dermatitis and asthma.² Our hypothesis in this study was whether or not emollients influence airway inflammation via skin barrier enhancement in young children in a real-world setting.

This was a cross-sectional study of well-child visits in Tokyo and Osaka, Japan. Target populations were caregivers who brought their children at the age of 1.5 years (~2,000 caregivers) and 3 years (~2000 caregivers) to the Osakasayama City Healthcare Center (Osaka, Japan) and Hino City Healthcare Center (Tokyo, Japan) from January 2020 to January 2021. The study was approved by the National Center for Child Health and Development (no. 995). This study obtained informed consent following the Ethical Guidelines for Epidemiological Research proposed by the Japanese Ministry of Health, Labour and Welfare. The caregivers answered a paper-based questionnaire about their children's life and allergic features. All outcomes (wheeze and asthma), exposures (emollients) and background information were evaluated based on the questionnaire. The prevalence of wheeze and asthma was assessed using the International Studies of Asthma and Allergies in Childhood (ISAAC) questionnaire at ages 1.5 and 3 years. The data did not contain personal information to maintain patient confidentiality, and a contract company performed data management. Regarding statistical analysis, possible associations between the frequency of reported emollient use and child and parent factors were determined using Fisher's exact test for discrete variables and one-way analysis of variance for continuous variables. p -value < .05 was considered statistically significant. Then, we conducted logistic regression analyses in which all potential confounders (delivery mode, pet ownership, sex, maternal educational level, smoking at home, sibling, parental allergic history, >6-month itchy rash and atopic dermatitis diagnosis) were included. In the statistical analysis plan defined before data fixation, confounders were selected in the order of relevance of the outcome and exposure in the target population, with reference to the literature

Key Messages

- We surveyed emollient use and wheeze and asthma in the children of well-child visits in Osaka and Tokyo, Japan.
- Emollients were applied in 77.3% of children at 1.5 years old and 59.8% at 3 years.
- Emollient use was more common in asthmatic children but was not associated with wheeze at 3 years of age.

and medical viewpoints. We also considered the issue of overfitting. We evaluated the adjusted odds ratios (aORs) and odds ratios (ORs) as measures of association and calculated 95% confidence intervals (CIs) and p values. The group with the highest frequency of emollient exposure was the once-daily application group, so the reference group was the group with once-daily application of emollients. All statistical analyses were performed using R statistical software, version 3.6.3 (The R Foundation) by an independent biostatistician (KP).

We obtained data from 380 and 236 caregivers of children aged 1.5 years and 385 and 207 caregivers of children aged 3 years who visited clinics in Osaka and Tokyo, respectively. Overall, the response rate (response number/target population number) was 30.8% and 29.6% at 1.5 and 3 years of age, respectively.

Table 1 shows the demographic features associated with emollient use in this study. Wheezing was prevalent in 14.6% (90/616) and 24.5% (145/592) of children at 1.5 and 3 years old, respectively. Asthma was prevalent in 9.8% (58/592) of 3-year-old children. More than half of the children had received emollient applications (77.3% and 59.8% at 1.5 and 3 years old, respectively). Sex and parental allergic history at 3 years of age and sibling at 1.5 years of age, >6-months itchy rash and atopic dermatitis diagnosis at 1.5 and 3 years of age were statistically different. There were no significant differences between moisturizing frequencies in terms of pet at home, smoking at home, delivery mode, gestational age, maternal educational level, parental age, breastfeeding duration and daycare centre.

Table 2 demonstrates the results of associations of wheeze and asthma with emollient application on the skin. Although there was

TABLE 1 Factors associated with emollient application

Moisturizing		1.5 years old (N = 616)				3 years old (N = 592)			
		Less than daily	Once daily	More than once daily	p-Value	Less than daily	Once daily	More than once daily	p-Value
Number of children		N = 140	N = 388	N = 88		N = 238	N = 300	N = 54	
Outcomes									
Asthma	Yes, n (%)	n/a	n/a	n/a		22 (9.2%)	25 (8.3%)	11 (20.4%)	.0357
Wheezing	Yes, n (%)	17 (12.1%)	64 (16.5%)	9 (10.2%)	.2351	51 (21.4%)	76 (25.3%)	18 (33.3%)	.1762
Adjusted confounders									
Sex	Boy, n (%)	83 (59.3%)	189 (48.7%)	50 (56.8%)	.0764	125 (52.5%)	170 (56.7%)	20 (37.0%)	.0279
Sibling	Yes, n (%)	91 (65.0%)	209 (53.9%)	36 (40.9%)	.0018	180 (75.6%)	220 (73.3%)	42 (77.8%)	.7049
Pet at home	Yes, n (%)	20 (14.3%)	64 (16.5%)	14 (15.9%)	.8628	35 (14.7%)	50 (16.7%)	11 (20.4%)	.5701
Smoking at home	Yes, n (%)	39 (27.9%)	104 (26.8%)	27 (30.7%)	.7700	68 (28.6%)	79 (26.3%)	11 (20.4%)	.4298
Atopic dermatitis	Yes, n (%)	0 (0.0%)	37 (9.5%)	14 (15.9%)	<.0001	11 (4.6%)	40 (13.3%)	12 (22.2%)	<.0001
Itchy rash lasting for more than 6 months	Yes, n (%)	11 (7.9%)	89 (22.9%)	32 (36.4%)	<.0001	32 (13.4%)	96 (32.0%)	18 (33.3%)	<.0001
Delivery mode	Vaginal delivery, n (%)	107 (76.4%)	308 (79.4%)	71 (80.7%)	.6609	192 (80.7%)	256 (85.3%)	45 (83.3%)	.3459
Parental allergic history	Yes, n (%)	82 (58.6%)	260 (67.0%)	60 (68.2%)	.2025	145 (60.9%)	209 (69.7%)	42 (77.8%)	.0499
Maternal Education level	Middle school or high school, n (%)	29 (20.7%)	64 (16.5%)	11 (12.5%)	.4845	41 (17.2%)	61 (20.3%)	6 (11.1%)	.5761
	Technical school or college, n (%)	47 (33.6%)	133 (34.3%)	35 (39.8%)		90 (37.8%)	109 (36.3%)	22 (40.7%)	
	University or graduate school, n (%)	59 (42.1%)	183 (47.2%)	42 (47.7%)		101 (42.4%)	127 (42.3%)	26 (48.1%)	
Unadjusted factors									
Paternal age	Mean (SD)	35.7 (5.6)	35.3 (5.9)	36.1 (5.6)	.4856	37.0 (5.3)	37.0 (5.4)	37.5 (5.5)	.8199
Maternal age	mean (SD)	33.8 (4.8)	33.4 (5.0)	33.5 (4.2)	.7126	35.6 (4.9)	35.2 (4.7)	35.8 (4.5)	.5781
Gestational age	37–41 weeks, n (%)	128 (91.4%)	347 (89.4%)	82 (93.2%)	.8773	208 (87.4%)	265 (88.3%)	48 (88.9%)	.7846
Parental nationality	Japanese, n (%)	136 (97.1%)	378 (97.4%)	86 (97.7%)	.6262	225 (94.5%)	291 (97.0%)	53 (98.1%)	1.0000
Breastfeeding duration	0–5 months, n (%)	25 (17.9%)	73 (18.8%)	13 (14.8%)	.9155	28 (11.8%)	36 (12.0%)	6 (11.1%)	.5021
	6–10 months, n (%)	28 (20.0%)	80 (20.6%)	19 (21.6%)		51 (21.4%)	54 (18.0%)	6 (11.1%)	
	11 months-, n (%)	79 (56.4%)	213 (54.9%)	53 (60.2%)		150 (63.0%)	202 (67.3%)	39 (72.2%)	
Day care	Yes, n (%)	67 (47.9%)	173 (44.6%)	43 (48.9%)	0.6554	193 (81.1%)	241 (80.3%)	45 (83.3%)	.7085

Note: Fisher's exact test was used for discrete variables, and one-way analysis of variance was used for continuous variables. n/a; not applicable. Bold; p-value < .05.

TABLE 2 Associations of wheeze and asthma with emollient application

Outcomes	Populations (N)	Exposures	Frequency of outcomes (%)	Crude odds ratio (95% CI)	p-Value	Adjusted odds ratio# (95% CI)	p-Value
Wheeze at 1.5 years old	All (N = 615)	Emollient application	Less than once daily	17/139 (12.2%)	0.71 (0.40–1.25)	0.63 (0.33–1.19)	.1549
			Once daily	64/388 (16.5%)	Reference	-	-
			More than once daily	9/88 (10.2%)	0.58 (0.28–1.21)	0.57 (0.26–1.23)	.1492
Wheeze at 3 years old	All (N = 590)	Emollient application	Less than once daily	51/236 (21.6%)	0.81 (0.54–1.22)	0.78 (0.50–1.23)	.2848
			Once daily	76/300 (25.3%)	Reference	-	-
			More than once daily	18/54 (33.3%)	1.47 (0.79–2.75)	1.62 (0.84–3.12)	.1530
Asthma at 3 years old	All (N = 590)	Emollient application	Less than once daily	22/236 (9.3%)	1.13 (0.62–2.06)	1.36 (0.72–2.59)	.3443
			Once daily	25/300 (8.3%)	Reference	-	-
			More than once daily	11/54 (20.4%)	2.81 (1.29–6.13)	2.78 (1.21–6.38)	.0158

#Adjusted confounding factors: delivery mode, pet ownership, sex, maternal educational level, smoking at home, sibling, parental allergic history, >6-months itchy rash and atopic dermatitis diagnosis. Statistically significant results shown in bold font.

a possible association between frequent emollient application and asthma at the age of 3 years (aOR: 2.78; 95% CI: 1.21–6.38), this was not supported by findings reported for the outcome of wheeze at the age of 1.5 or 3 years and may be explained by confounding factors that went unobserved. Perkin and colleagues³ reported that moisturizing increased the risk of food allergy, which was consistent with our results. Frequent moisturizing might be a possible risk factor for developing allergic diseases, such as food allergy and asthma. Parabens are preservative ingredients found in emollients. Children with atopic dermatitis were highly exposed to paraben from the previous study,⁴ and paraben increased the risk of immunoglobulin E sensitization from the US study.⁵

Our study indicated that the application of emollients on the skin did not affect wheezing but increased asthma events in young children at 3 years of age from a cross-sectional study of well-child visits. We found that 77.3% and 59.8% of children aged 1.5 and 3 years had been treated with emollient application. We attributed these percentages to widespread distribution of reports of a randomized control study (RCT)⁶ in Japan confirming that skincare intervention applied as early as the neonatal period could prevent eczema. Most childcare magazines of Japan state that moisturizers should be applied starting from the neonatal period. The strength of our study was that we could conduct this study in the field of a well-child visit, which means that we could recruit general populations to minimize sampling bias. Although we did not perform an interventional study, our study results reflect the real-world setting. There were several limitations to this study: first, although we adjusted for potential confounding factors when evaluating the associations between exposures (emollients) and outcomes (wheeze and asthma), it was difficult to prove causal relationships due to the cross-sectional nature of the study. It was impossible to evaluate the duration and timing of emollient application, but widespread research results⁶ demonstrated that skincare intervention was initiated during the neonatal period due to the moisturizing campaign by most childcare magazines, as previously mentioned. Therefore, we believe that almost all children might start emollient application during the neonatal period. It was also possible that the number of cases might be insufficient for obtaining the incidence rates for outcome events and that the influence of these findings might also be insufficient. Not all caregivers answered our questionnaire. Due to the COVID-19 epidemic, certain caregivers avoided bringing their children to well-child visits. Only caregivers who were interested in this study might have participated.

Although our study group previously demonstrated that skincare intervention with emollients could prevent the development of eczema in young infants from an RCT,⁶ emollient interventions have shown controversial results against the prevention of eczema and food allergy based on a recently published systematic review.⁷ Lowe and colleagues⁸ demonstrated that a twice-daily sufficient amount of high-quality emollient application tended to reduce atopic dermatitis and allergen sensitization. Morita and colleagues demonstrated that epicutaneously allergen-sensitized mice induced type 2 airway inflammation.⁹ Type 2 immunity in the skin

and lungs is related.² We propose that skincare intervention might be beneficial for specific populations and purposes (e.g., high-risk eczema infants).

KEYWORDS

asthma, emollients, skin barrier, well-child visit, wheeze

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare related to this study.

AUTHOR CONTRIBUTION

KYH was the principal investigator. KYH, MS, YE, YT, NI and YO contributed to the conception or design of the work, data collection and interpretation and drafting the manuscript. KP conducted data analyses. All authors agreed to publish the final version of this manuscript.

ETHICAL APPROVAL

The study protocol was reviewed and approved by the ethical committee of the National Center for Child Health and Development and the University of Tokyo (number 995). This study obtained informed consent following the Ethical Guidelines for Epidemiological Research proposed by the Ministry of Health, Labour and Welfare of Japan.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Kiwako Yamamoto-Hanada¹ 

Kyongsun Pak² 

Miori Sato¹

Yuri Endo Kram¹ 

Yutaka Takemura³

Norihiro Inoue⁴

Yukihiro Ohya¹ 

¹Allergy Center, National Center for Child Health and Development, Setagaya, Tokyo, Japan

²Division of Biostatistics, Department of Data Management,
Center for Clinical Research and Development, National
Center for Child Health and Development, Setagaya, Tokyo,
Japan

³Department of Pediatrics, Kindai University Faculty of
Medicine, Osakasayama, Osaka, Japan

⁴Department of Pediatrics, National Hospital Organization
Osaka Minami Medical Center, Kawachinagano, Osaka, Japan

Correspondence

Kiwako Yamamoto-Hanada, Chief, Allergy Center, National
Center for Child Health and Development, 2-10-1, Okura,
Setagaya, Tokyo, 157-8535, Japan.
Email: yamamoto-k@ncchd.go.jp

ORCID

Kiwako Yamamoto-Hanada  <https://orcid.org/0000-0003-1288-9620>

Kyongsun Pak  <https://orcid.org/0000-0002-0934-8949>

Yuri Endo Kram  <https://orcid.org/0000-0003-2058-7083>

Yukihiro Ohya  <https://orcid.org/0000-0002-1560-3942>

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