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Letter to the Editor

Four phenotypes of atopic dermatitis in Japanese children: A general population birth cohort study

Dear Editor,

Atopic dermatitis (AD) is a common skin disease characterized by a chronic eczematous skin disorder with pruritus.¹ A nationwide birth cohort study in Japan found that 15.7% of pregnant women had a past history of AD diagnosis.² A European cohort study identified the allergic features of AD and found that the presentations of wheezing and rhinitis varied in the allergic march.³ Capturing phenotypes identified by different trajectories could lead to personalized precision medicine. Although our research team previously reported five phenotypes of wheezing in Japanese children in a prospective birth cohort study,⁴ the AD phenotypes in Japanese children have never been determined. The aim of this study was therefore to identify the AD phenotypes and to assess the associated risk factors in Japanese children.

This general prospective birth cohort study, called the Tokyo Children's Health, Illness and Development study (T-CHILD study), was conducted at the National Center for Child Health and Development (NCCHD).⁵ In total, 1701 pregnant women were recruited at the NCCHD between 2003 and 2005, and 1550 of their offspring were followed. The study was approved by the Institutional Review Board of the NCCHD (No. 52). Informed consent was obtained from all the participants. To collect background information, the caregivers were asked to complete a paper-based questionnaire. Sensitization to common allergens was analyzed by ImmunoCAP-ISAC (<http://www.inter-2t.phadia.com/ja/9/2/ImmunoCAP-ISAC/>) for ages 5 and 9 years, and AD was diagnosed by physicians using the U.K. working party's diagnostic criteria (UKWP) for ages 5 and 9 years. For the trajectory analysis, AD was assessed at approximately one-year intervals based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.⁶ The trajectories were analyzed using the AD data for children aged 0.5–9 years. In total, 1157 children whose parents responded to the questionnaires on their children's AD symptoms on at least seven occasions were enrolled for analysis. The trajectories were identified using the group-based trajectory modeling (GBTM) approach as in a previous report.⁴ All the analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC). SAS Traj, an SAS macro that estimates a discrete mixture model for clustering of longitudinal data series, was used for all modeling processes (<https://www.andrew.cmu.edu/user/bjones/>).

The children between age 0.5 and 9 years with at least seven responses for atopic dermatitis are shown in [Supplementary Table 1](#).

Of 1157 children, 49.4% were female, and 20.4% had a parental history of AD. We identified four AD trajectory phenotypes ([Fig. 1](#)), including the never/infrequent (62.7%), early-onset (17.6%), late-onset (9.5%), and persistent (10.1%) phenotypes. [Table 1](#) shows the patient characteristics by trajectory. Children with persistent AD had a higher proportion of parental history of AD (40.2% vs. 14.4%), higher sensitization to common allergens at age 9 years (96.1% vs. 67.5%), and AD more frequently diagnosed by physicians based on the UKWP at 9 years old (91.0% vs. 9.5%) than children with never/infrequent AD. In particular, persistent AD was more highly associated with a family history of AD and asthma and a higher degree of sensitization. In the PASTURE study, Roduit *et al.*⁷ identified four AD phenotypes in a European cohort, in line with our own findings. They also reported that the prevalence of the phenotypes was 9.2% for early transient AD, 6.5% for early persistent AD, 4.8% for later AD, and 79.5% for never/infrequent AD. In comparison, we found a higher prevalence of early-onset, persistent AD and late-onset AD in our cohort. This may be due to the participants bias in this cohort such as high-income family and urban living. In addition, Paternoster *et al.* identified six AD phenotypes in two other European cohort studies (ALSPAC and PIAMA Studies).⁸ This discrepancy in the number of phenotypes might be due to variations in the study populations and design. Nonetheless, AD is a heterogeneous disease,⁹ and further research is needed to clarify the current evidence of AD phenotypes.

To the best of our knowledge, this may be the first study to identify four AD phenotypes using the group-based trajectory modeling (GBTM) approach in Japanese children. The strength of the study lies in the analysis of the AD trajectories using data from the general population in a prospective longitudinal cohort study design.

Our study has some limitations. First, atopic dermatitis was not diagnosed by a physician, but was determined on the basis of responses given by the caretakers on the ISAAC questionnaire.⁶ Thus the prevalence of AD might have been underestimated. However, the questionnaire was validated for use with patients with AD and has international epidemiological currency. Second, we were unable to analyze some of the data, such as the variables related to biomarkers, because we did not obtain biological samples from the infants. We examined only children. Silverberg *et al.* reported that adult-onset AD had different phenotypes than childhood-onset AD.¹⁰ We hope to see future, long-term, cohort studies following children from early childhood to adulthood to clarify the AD phenotypes, including the characteristics of adult AD.

Peer review under responsibility of Japanese Society of Allergy.

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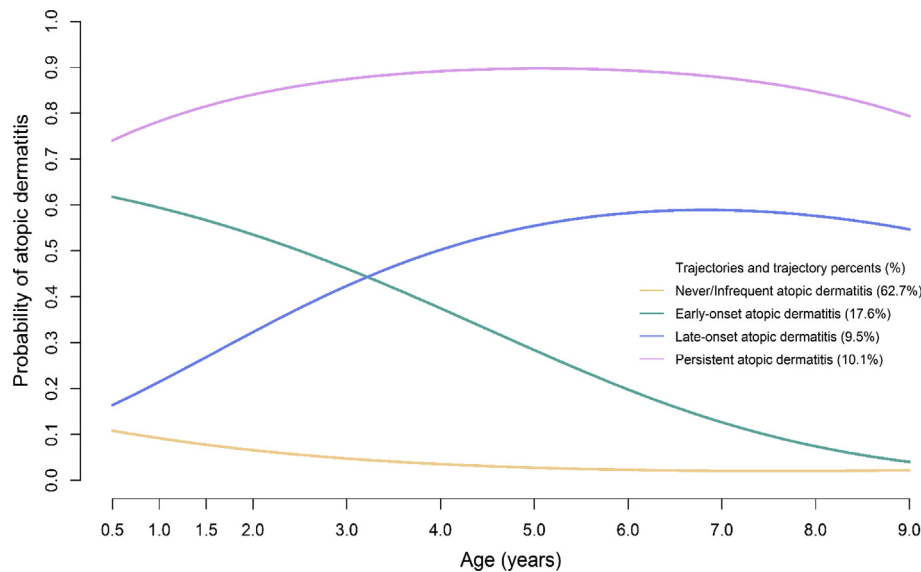


Fig. 1. Estimated prevalence of AD at each age between 0.5 and 9 years for each of the four AD phenotypes identified by group-based.

Table 1
Children's characteristics by AD trajectory.

	Never/infrequent AD	Early-onset AD	Late-onset AD	Persistent AD
	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Sex (female)	51.3% (389/758)	42.0% (76/181)	44.7% (46/103)	53.0% (61/115)
Parental history of AD	14.4% (107/741)	27.7% (49/177)	29.0% (29/100)	40.2% (45/112)
Parental history of asthma	20.9% (156/748)	22.5% (40/178)	23.0% (23/100)	34.8% (39/112)
Sensitization to allergen components at 5 years old	48.5% (300/618)	73.4% (105/143)	63.5% (54/85)	87.9% (80/91)
Sensitization to allergen components at 9 years old	67.5% (316/468)	85.3% (99/116)	81.8% (54/66)	96.1% (73/76)
AD by UKWP at 5 years old	10.3% (64/624)	52.4% (77/147)	68.6% (59/86)	95.9% (93/97)
AD by UKWP at 9 years old	9.5% (45/473)	30.5% (36/118)	65.7% (44/67)	91.0% (71/78)
AD by ISAAC at 9 years old	4.0% (23/576)	18.4% (26/141)	31.3% (26/83)	71.3% (72/101)

AD, atopic dermatitis; UKWP, the U.K. working party's diagnostic criteria; ISAAC, International Study of Asthma and Allergies in Childhood.

In conclusion, we identified four phenotypes of childhood AD trajectory in Japanese children using the group-based trajectory modeling approach, including the never/infrequent (62.7%), early-onset (17.6%), late-onset (9.5%), and persistent (10.1%) phenotypes. AD presentation in Japanese children was also heterogeneous. We look forward to future studies on therapeutic strategies based on these AD phenotypes.

Acknowledgements

We deeply thank the mothers and children who participated in the T-CHILD Study. We also wish to thank the medical editors from the Division of Education for Clinical Research at the National Center for Child Health and Development for editing this manuscript. This study was supported by a grant from the National Center for Child Health and Development (26–18).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.02.010>.

Conflict of interest

The authors have no conflict of interest to declare.

Kiwako Yamamoto-Hanada ^{a,b,*}, Limin Yang ^{a,b}, Mayako Saito-Abe ^{a,b}, Miori Sato ^{a,b}, Yusuke Inuzuka ^a, Kenji Toyokuni ^a, Koji Nishimura ^a, Makoto Irahara ^a, Fumi Ishikawa ^a, Yumiko Miyaji ^a, Tatsuki Fukuie ^a, Masami Narita ^a, Hirohisa Saito ^c, Yukihiro Ohya ^{a,b}

^a Allergy Center, National Center for Child Health and Development, Tokyo, Japan

^b Medical Support Center for the Japan Environment and Children's Study, Research Institute, National Center for Child Health and Development, Tokyo, Japan

^c Department of Allergy and Immunology, Research Institute, National Center for Child Health and Development, Tokyo, Japan

* Corresponding author. Allergy Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.
E-mail address: yamamoto-k@ncchd.go.jp (K. Yamamoto-Hanada).

References

1. Furue M, Chiba T, Tsuji G, Ulzii D, Kido-Nakahara M, Nakahara T, et al. Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. *Allergol Int* 2017;**66**:398–403.
2. Yamamoto-Hanada K, Yang L, Ishitsuka K, Ayabe T, Mezawa H, Konishi M, et al. Allergic profiles of mothers and fathers in the Japan Environment and Children's Study (JECS): a nationwide birth cohort study. *World Allergy Organ J* 2017;**10**:24.
3. Belgrave DC, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. *PLoS Med* 2014;**11**:e1001748.
4. Yang L, Narita M, Yamamoto-Hanada K, Sakamoto N, Saito H, Ohya Y. Phenotypes of childhood wheeze in Japanese children: a group-based trajectory analysis. *Pediatr Allergy Immunol* 2018;**29**:606–11.

5. Yamamoto-Hanada K, Futamura M, Yang L, Shoda T, Narita M, Kobayashi F, et al. Preconceptional exposure to oral contraceptive pills and the risk of wheeze, asthma and rhinitis in children. *Allergol Int* 2016;**65**:327–31.
6. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and Allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–91.
7. Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrlander C, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatr* 2017;**171**:655–62.
8. Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J Allergy Clin Immunol* 2018;**141**:964–71.
9. Nakamura T, Haider S, Custovic A. Understanding the heterogeneity of atopic dermatitis in childhood. *Curr Allergy Clin Immunol* 2018;**31**:124–30.
10. Silverberg JI, Vakharia PP, Chopra R, Sacotte R, Patel N, Immaneni S, et al. Phenotypical differences of childhood- and adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract* 2018;**6**:1306–12.

Received 30 January 2019

Received in revised form 16 February 2019

Accepted 20 February 2019

Available online xxx

Supplementary Table 1. Children with at least seven responses for AD between ages 0.5 and 9 years

	Total	n	%
Sex (female)	1157	572	49.4
Parental history of AD	1130	230	20.4
Parental history of asthma	1138	258	22.7
Prevalence of AD in children			
0.5 years	1131	269	23.8
1 year	1135	313	27.6
1.5 years	1140	320	28.1
2 years	1130	274	24.2
3 years	1100	290	26.4
4 years	1097	233	21.2
5 years	1125	240	21.3
6 years	1074	172	16
7 years	916	185	20.2
8 years	897	163	18.2
9 years	901	146	16.2

AD, atopic dermatitis.