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Persistent eczema leads to both impaired growth and food allergy: JECS birth cohort

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Abstract

Skin inflammation leads to altered cytokine/chemokine production and causes systemic inflammation. The systemic mechanism of atopic dermatitis (AD) is recognized to affect systemic metabolism. This study aimed to examine the relationship between early-onset persistent eczema and body weight, height, and body mass index (BMI), in addition to food allergy in a birth cohort among infants. This study design was a nationwide, multicenter, prospective birth cohort study—the Japan Environment and Children's Study (JECS). Generalized linear models were fitted for z scores of weight, height, BMI, and food allergy to evaluate the relationship between eczema and these outcomes for infants at age1, 2, and 3 years. Persistent eczema was negatively associated with height at the age of 2 years (estimated coefficient, −0.127; 95% confidence interval [CI], −0.16 to −0.095) and 3 years (−0.177; 95% CI, −0.214 to −0.139). The same tendency was also observed with weight and BMI. Early disease onset at younger than 1 year and persistent eczema had the strongest association with development of food allergy at age 3 years (OR, 11.794; 95% CI, 10.721–12.975). One phenotype of eczema with early-onset and persistent disease creates a risk of both physical growth impairment and development of food allergy. Infants who present with the early-onset and persistent type of eczema should be carefully evaluated daily for impaired physical growth and development of food allergy.

Introduction

Atopic dermatitis (AD) is characterized by chronic skin inflammation and heterogeneous disease [1]. Several studies reported several phenotypes of AD in children [2, 3]. In Japan, 7.3% young children were diagnosed as AD from a national birth cohort [4]. AD is associated with

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various comorbidities such as anxiety, depression, and attention deficit hyperactivity disorder [5, 6]. Skin inflammation leads to altered cytokine/chemokine production and causes systemic inflammation [7]. Thereby, the systemic mechanism of AD is recognized to affect systemic metabolism. Nomura et al. [8] reported that infants hospitalized with severe AD had impaired mental and physical growth, protein loss through skin inflammation, and elevated serum interleukin (IL), including IL5, IL6, and IL12. Furthermore, early-onset and/or persistent AD is a known risk factor for food allergy based on a birth cohort study [3, 9]. We hypothesized that early-onset and persistent AD in infants may lead not only to impaired physical growth but food allergy as well because of long-term skin inflammation. This study aimed to examine the relationship between early-onset persistent AD and body weight, height, and body mass index (BMI), in addition to food allergy in a birth cohort.

Materials and methods

This study design was a nationwide, multicenter, prospective birth cohort study—the Japan Environment and Children's Study (JECS), funded by the Ministry of the Environment, Japan [10–12]. The JECS enrolled a general population of 103,060 pregnant women in 15 Study Areas covering a wide region across Japan from the north (Hokkaido) to south (Okinawa) from January 2011 to March 2014. Eligibility criteria were as follows: 1) currently pregnant; 2) living in the Study Area for the foreseeable future; 3) expected delivery between August 1, 2011, and mid-2014; and 4) ability to understand the Japanese language. In total, 104,062 fetuses were enrolled in the JECS. The registry of the JECS is the University Hospital Medical Information Network (UMIN Clinical Trials Registry 000030786). The JECS protocols for the main study and the sub-cohort study are described on the websites of the Ministry of the Environment, Japan [13, 14]. The JECS protocol was reviewed and approved by the Ministry of Environment's Institutional Review Board for Epidemiologic Studies (#100910001) and by the ethics committees of all participating institutions (#2019–070). Written informed consent was obtained from all participants. The JECS was conducted in accordance with the principles laid out in the Helsinki Declaration and other national regulations and guidelines.

Questionnaire

Written questionnaires were provided to caregivers during pregnancy for child participants at age 6 months and 1, 1.5, 2, 2.5, and 3 years. Caregivers answered questions regarding the child and the family.

Outcomes

Information on each child's background and lifestyle was assessed using questionnaires in Japanese. Eczema history and Caregiver-reported physician diagnoses food allergy were obtained from questionnaires at ages 1, 2, and 3 years.

This study extracted the children's weight and height data from surveys conducted at age 1, 2, and 3 years. The LMS (lambda-mu-sigma) statistical method was used to calculate z scores for weight, height, and BMI (weight/height2) [15]. Age- and sex-specific values of L, M, and S were obtained from the Japanese growth curve criteria [16, 17].

Statistical analyses

After excluding preterm birth, twin birth, neonatal complications, and chronic disease other than eczema and food allergy, 59,847 mother–child pairs remained for analysis (S1 Fig). A

fixed data set (jecs-ta-201901930-qsn, released in October 2019) was used for this study. Generalized linear models were fitted for z scores of weight, height, BMI, and food allergy. An identity link function was used to model continuous outcomes (z scores of weight, height, BMI), and a logit link was used for modeling the binary outcome (food allergy). The coefficients in the models provided measures for the strength of associations (compared with the reference group). Three models were fitted for each outcome (z scores of weight, height, BMI, and food allergy) for children at ages 1, 2, and 3 years. For the models evaluating the relationship between eczema and outcomes for children at age 2 years, the exposure variable eczema was classified into four groups: 1) no eczema at 1 and 2 years; 2) eczema at 1–2 years; 3) eczema only at 1 year; and 4) eczema only at 2 years. The group that had no eczema at age 1 and 2 years was designated as reference group. Similarly, on assessment at age 3 years, children with eczema during 1–3 years had eight patterns based on whether they had eczemaat age 1, 2, and 3 years or not. The status of no eczema at 1, 2, and 3 years was designated as reference group in the models. Eczema and food allergy are high multicollinearity so we did not input food allergy in the models. An assumption was made that data were missing at random. Missing data for independent variables were imputed using multiple imputation (MI) analysis with a chained equations (MICE) algorithm. The variables used for MI process included sex, siblings, maternal history of AD, paternal history of AD, and maternal highest level of education. To obtain pooled coefficients of models, 20 data sets with missing data were generated. Bonferroni correction was applied for correcting multiple testing, and the thresholds were set at 0.05/44 (0.001). For the sensitivity analysis, the same models were refitted using complete dataset.

All the analyses were performed using R software (version 4.0.3, Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). The R packages "MICE" was used for the MI process.

Results

Table 1 shows the baseline characteristics. Maternal history of AD was found for 15.8% of participants. Income: <4,000,000 yen/annual income was reported from 38.8 participants.

Table 2 presents the numbers of participants with AD and food allergy. At the age of 1 year, 19% infants had AD and food allergy. At the age of 3 years, 27.7% infants had persistent AD and food allergy. Most cases of AD at the age of 1 year were transient.

Table 3 presents the eczema associations with z scores of body weight, height, and BMI at ages 1, 2, and 3 years. Early disease onset at younger than 1 year and persistent eczema were evaluated for association with the child's status at ages 2 and 3 years as follows. Body weight was negatively associated with persistent eczema at the age of 2 years (estimated coefficient, −-0.146; 95% confidence interval [CI], −0.174 to −0.117) and 3 years (−0.148; 95% CI, −0.181 to −0.114). Height was negatively associated with persistent eczema at the age of 2 years (estimated coefficient, −0.127; 95% CI, −0.16 to −0.095) and 3 years (−0.177; 95% CI, −0.0214 to −-0.139). Also, BMI was negatively associated with height at the age 2 years (estimated coefficient, −0.081; 95% CI, −0.113 to −0.05) and 3 years (−0.058; 95% CI, −0.094 to −0.022).

Table 4 shows the associations of eczema with food allergy. Early disease onset at younger than 1 year and persistent eczema had the strongest association with development of food allergy at age 2 years (odds ratio [OR], 9.861; 95% CI, 9.115–10.668) and 3 years (OR, 11.794; 95% CI, 10.721–12.975). Late onset of eczema (diagnosis at three years of age) was less associated with food allergy development (OR, 2.373; 95%CI, 2.02–2.789) compared to the early-onset and persistent eczema.

Table 1. Baseline characteristics for participants.

Participant	n	N	%
Place at recruitment			
Hokkaido	4570	59847	7.6
Miyagi	5196	59847	8.7
Fukushima	7929	59847	13.2
Chiba	3110	59847	5.2
Kanagawa	3916	59847	6.5
Koshin	4245	59847	7.1
Toyama	3377	59847	5.6
Aichi	3343	59847	5.6
Kyoto	2512	59847	4.2
Osaka	4791	59847	8
Hyogo	3147	59847	5.3
Tottori	1877	59847	3.1
Kochi	4075	59847	6.8
Fukuoka	4424	59847	7.4
South Kyushu/Okinawa	3335	59847	5.6
Mother			
Age <35 years	44473	59577	74.6
Age > = 35 years	15104	59577	25.4
Education: Middle school and high school	20144	59319	34
Education: Technical, College, University and Graduate	39175	59319	66
Income: <4,000,000 yen/annual income	21640	55768	38.8
Income: > = 4,000,000 yen/annual income	34128	55768	61.2
Health: Maternal atopic dermatitis history (+)	9400	59580	15.8
Health: Maternal food allergy history (+)	2793	59580	4.7
Child			
Sibling	33766	59580	56.7
Boys	30051	59847	50.2
Girls	29796	59847	49.8

n, yes, N, variables without missing data.

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Discussion

Based on these data from a large-scale, national, birth cohort study in Japan, early-onset and persistent eczema negatively affected physical growth and created a risk of low body weight, short height, low BMI, and development of food allergy. To the best of our knowledge, this is the first report on the relationship between infant eczema and physical growth among the Japanese general population. We demonstrated that early-onset and persistent eczema phenotype was the strongest risk factor for both physical growth retardation and food allergy. This is also the first report regarding the mechanism by which eczema phenotypes are linked to body weight, height, and BMI. A systematic review and meta-analysis [18] of AD and weight status in children observed that AD overall was associated with overweight (random effects OR, 1.24; 95% CI, 1.08–1.43), obesity (random effects OR, 1.44; 95% CI, 1.12–1.86), or overweight/obesity (random effects OR, 1.32; 95% CI, 1.15–1.51). This systematic review included all phenotypes of AD, which is a heterogeneous disease with several phenotypes [2, 3]. The associations of comorbidity, such as allergic diseases—food allergy, asthma, and immunoglobulin E

Table 2. Number of participants with AD and FA.

Child (age in years)	FA (–)		FA (+)	
	n	(%)	n	(%)
1 year of age				
eczema1Y (–)	46065	96.2	1809	3.8
eczema1Y(+)	8861	81	2082	19
Missing	246	–	15	–
ALL	55172	93.4	3906	6.6
2 years of age				
eczema1Y(–) and eczema2Y(–)	41592	96.5	1518	3.5
eczema1Y(+) and eczema2Y(+)	3832	72.6	1448	27.4
eczema1Y(–) and eczema2Y(+)	4093	89.8	465	10.2
eczema1Y(+) and eczema2Y(–)	4860	87	729	13
Missing	1203	–	107	–
ALL	55580	92.9	4267	7.1
3 years of age				
eczema1Y(–) and eczema2Y(–) and eczema3Y(–)	39143	97.2	1135	2.8
eczema1Y(+) and eczema2Y(+) and eczemaY(+)	2416	72.8	904	27.2
eczema1Y(+) and eczema2Y(+) and eczema3Y(–)	1504	80.7	360	19.3
eczema1Y(+) and eczema2Y(–) and eczema3Y(+)	834	82.5	177	17.5
eczema1Y(+) and eczema2Y(–) and eczema3Y(–)	4049	89.5	477	10.5
eczema1Y(–) and eczema2Y(+) and eczema3Y(+)	1592	87.9	220	12.1
eczema1Y(–) and eczema 2Y(+) and eczema3Y(–)	2509	93.2	182	6.8
eczema1Y(–) and eczema2Y(–) and eczema3Y(+)	2481	93.2	181	6.8
Missing	1523	–	160	–
ALL	56051	93.7	3796	6.3

ALL, participants including; FA, food allergy; 1Y, age 1 year; 2Y, age 2 years; 3Y, age 3 years.

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sensitization—differed among AD phenotypes. Adult populations with severe AD may gain weight after treatment with dupilumab [19]. Early-onset AD tended to be more severe disease [20]. A systematic review of 66 studies concluded that AD appeared to precede the development of food allergy. Therefore, we considered that AD occurs before food allergy. It is also known that AD can be a risk factor for developing IgE sensitization to allergens. We considered that eczema occurred first, sensitization second, and food allergy third based on the systematic review. The present study speculates that severe and persistent eczema may lead to persistent skin inflammation, producing various cytokines/chemokines from the skin that may in turn affect systemic metabolism. A previous study reported that severe childhood AD led to hypoprotenemia, hyperkaremia, and hyponatremia as leaking through the skin [8]. Homeostasis of the body could be damaged by skin inflammation. Early-onset and persistent eczema may create a risk of not only "allergic march" but also slowed physical growth. Multiple comorbidities related to eczema should be considered for this eczema phenotype [21].

In general, epidemiologic studies have limitations. Reporting biases inevitably arise. Outcome assessments were not made directly by clinicians but through a questionnaire given to caregivers. The prevalence and incidence of the disease may have been overestimated or underestimated. However, we could apply physician-diagnosis outcomes. Various past studies have used same definitions. Second, information regarding medical interventions, including medications, was not obtained, thus it was not possible to evaluate how medical interventions

Table 3. Caregiver-reported physician diagnoses of atopic dermatitis and physical growth.

Age (years)	Outcomes (z scores)		Eczema 1 year	Eczema 2 years	Eczema 3 years	Coefficient[a]	SE	95% CI		p value[b]
								Lower	Upper	
1	Weight	Eczema1Y (–)	–			1				
		Eczema1Y(+)	+			**–0.093**	**0.011**	**–0.114**	**–0.072**	**<0.0001**
2	Weight	Eczema 1Y(–) Eczema 2Y(–)	–	–		1				
		Eczema1Y(+) Eczema2Y(+)	+	+		**–0.146**	**0.015**	**–0.174**	**–0.117**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(+)	–	+		0.012	0.016	–0.018	0.042	0.4404
		Eczema1Y(+) Eczema2Y(–)	+	–		**–0.079**	**0.014**	**–0.107**	**–0.051**	**<0.0001**
3	Weight	Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(–)	–	–	–	1				
		Eczema1Y(+) Eczema2Y(+) Eczema3Y(+)	+	+	+	**–0.148**	**0.017**	**–0.181**	**–0.114**	**<0.0001**
		Eczema1Y(+) Eczema 2Y(+) Eczema3Y(–)	+	+	–	–0.067	0.022	–0.111	–0.023	0.0029
		Eczema1Y(+) Eczema 2Y(–) Eczema 3Y(+)	+	–	+	–0.019	0.03	–0.079	0.04	0.5230
		Eczema1Y(+) Eczema2Y(–) Eczema3Y(–)	+	–	–	**–0.058**	**0.015**	**–0.087**	**–0.029**	**0.000108**
		Eczema 1Y(–) Eczema 2Y(+) Eczema 3Y(+)	–	+	+	–0.037	0.023	–0.082	0.008	0.1068
		Eczema 1Y(–) Eczema 2Y(+) Eczema 3Y(–)	–	+		–0.011	0.019	–0.048	0.026	0.5487
		Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(+)	–	–	+	–0.005	0.019	–0.043	0.032	0.7718
1	Height	Eczema1Y (–)	–			1				
		Eczema1Y(+)	+			**–0.047**	**0.011**	**–0.068**	**–0.025**	**<0.0001**
2	Height	Eczema 1Y(–) Eczema 2Y(–)	–	–		1				
		Eczema1Y(+) Eczema2Y(+)	+	+		**–0.127**	**0.017**	**–0.16**	**–0.095**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(+)	–	+		–0.029	0.018	–0.064	0.005	0.0982591
		Eczema1Y(+) Eczema2Y(–)	+	–		–0.042	0.016	–0.074	–0.011	0.0088
3	Height	Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(–)	–	–	–	1				
		Eczema1Y(+) Eczema2Y(+) Eczema3Y(+)	+	+	+	**–0.177**	**0.019**	**–0.214**	**–0.139**	**<0.0001**
		Eczema1Y(+) Eczema 2Y(+) Eczema3Y(–)	+	+	–	–0.065	0.025	–0.114	–0.016	0.0098
		Eczema1Y(+) Eczema 2Y(–) Eczema 3Y(+)	+	–	+	–0.098	0.034	–0.165	–0.032	0.0038
		Eczema1Y(+) Eczema2Y(–) Eczema3Y(–)	+	–	–	–0.055	0.017	–0.088	–0.022	0.0010
		Eczema 1Y(–) Eczema 2Y(+) Eczema **3Y(+)**	–	+	+	**–0.095**	**0.025**	**–0.145**	**–0.045**	**0.0002**
		Eczema 1Y(–) Eczema 2Y(+) AD3Y(–)	–	+		–0.027	0.021	–0.068	0.014	0.2007
		Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(+)	–	–	+	–0.048	0.021	–0.09	–0.006	0.0246
1	BMI	Eczema1Y (–)	–			1				
		Eczema1Y(+)	+			**–0.069**	**0.011**	**–0.09**	**–0.048**	**<0.0001**
2	BMI	Eczema 1Y(–) Eczema 2Y(–)	–	–		1				
		Eczema1Y(+) Eczema2Y(+)	+	+		**–0.081**	**0.016**	**–0.113**	**–0.05**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(+)	–	+		0.049	0.017	0.015	0.082	0.0046
		Eczema1Y(+) Eczema2Y(–)	+	–		**–0.064**	**0.016**	**–0.094**	**–0.033**	**<0.0001**
3	BMI	Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(–)	–	–	–	1				
		Eczema1Y(+) Eczema2Y(+) Eczema3Y(+)	+	+	+	**–0.058**	**0.018**	**–0.094**	**–0.022**	**0.001483**
		Eczema1Y(+) Eczema 2Y(+) Eczema3Y(–)	+	+	–	–0.051	0.024	–0.098	–0.003	0.0367
		Eczema1Y(+) Eczema 2Y(–) Eczema 3Y(+)	+	–	+	0.053	0.033	–0.011	0.117	0.1064
		Eczema1Y(+) Eczema2Y(–) Eczema3Y(–)	+	–	–	–0.041	0.016	–0.072	–0.009	0.0118
		Eczema 1Y(–) Eczema 2Y(+) Eczema 3Y(+)	–	+	+	0.041	0.025	–0.008	0.089	0.1011
		Eczema 1Y(–) Eczema 2Y(+) Eczema 3Y(–)	–	+		0.007	0.02	–0.033	0.047	0.7271
		Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(+)	–	–	+	0.046	0.02	0.006	0.086	0.0253

AD, atopic dermatitis; CI, confidence interval; 1 Y, age 1 year; 2 Y, age 2 years; 3 Y, age 3 years.

[a]Generalized linear models with identity link function.

[b]Bonferroni correction was applied for correcting multiple testing, and the thresholds were set at 0.05/44 (0.001).

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Table 4. Caregiver-reported physician diagnoses of atopic dermatitis and food allergy.

Age (years)	Outcomes		Odds ratio	95% CI		p value[b]
				Lower	Upper	
1	Food allergy	Eczema1Y (–)	1			
		Eczema1Y(+)	**5.943**	**5.558**	**6.354**	**<0.0001**
2	Food allergy	Eczema 1Y(–) Eczema 2Y(–)	**1**			
		Eczema1Y(+) Eczema2Y(+)	**9.861**	**9.115**	**10.668**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(+)	**3.012**	**2.703**	**3.356**	**<0.0001**
		Eczema1Y(+) Eczema2Y(–)	**3.962**	**3.61**	**4.348**	**<0.0001**
3	Food allergy	Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(–)	**1**			
		Eczema1Y(+) Eczema2Y(+) Eczema3Y(+)	**11.794**	**10.721**	**12.975**	**<0.0001**
		Eczema1Y(+) Eczema 2Y(+) Eczema3Y(–)	**7.603**	**6.687**	**8.646**	**<0.0001**
		Eczema1Y(+) Eczema 2Y(–) Eczema 3Y(+)	**6.767**	**5.698**	**8.037**	**<0.0001**
		Eczema1Y(+) Eczema2Y(–) Eczema3Y(–)	**3.791**	**3.392**	**4.236**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(+) AD3Y(+)	**4.428**	**3.797**	**5.163**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(+) AD3Y(–)	**2.366**	**2.013**	**2.782**	**<0.0001**
		Eczema 1Y(–) Eczema 2Y(–) Eczema 3Y(+)	**2.373**	**2.02**	**2.789**	**<0.0001**

CI, confidence interval; 1 Y, age 1 year; 2 Y, age 2 years; 3 Y, age 3 years.

[a]Generalized linear models with Logit link function (logistic regression model).

[b]Bonferroni correction was applied for correcting multiple testing, and the thresholds were set at 0.05/44 (0.001).

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and disease activities may affect physical growth and food allergy. In terms of for the elimination status, we did not evaluate the details of the elimination diet. However, we believe that the Japanese guidelines on food allergy recommend minimum causal food elimination; thus, we considered that most children underwent only minimum food elimination that did not affect physical growth.

Conclusions

This study highlighted that one phenotype of eczema with early-onset and persistent disease creates a risk of both physical growth impairment and development of food allergy. Infants who present with the early-onset and persistent type of eczema should be carefully evaluated daily for impaired physical growth and development of food allergy.

Supporting information

S1 Fig. Flow chart of the study participants.
(DOCX)

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References

1. Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin-Weller M, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020; 34(12):2717–44. Epub 2020/11/19. https://doi.org/10.1111/jdv.16892 PMID: 33205485.
2. Yamamoto-Hanada K, Yang L, Saito-Abe M, Sato M, Inuzuka Y, Toyokuni K, et al. Four phenotypes of atopic dermatitis in Japanese children: A general population birth cohort study. Allergol Int. 2019; 68 (4):521–3. Epub 2019/04/03. https://doi.org/10.1016/j.alit.2019.02.010 PMID: 30935805.
3. 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 (7):655–62. https://doi.org/10.1001/jamapediatrics.2017.0556 PMID: 28531273.

4. Yamamoto-Hanada K, Pak K, Saito-Abe M, Yang L, Sato M, Irahara M, et al. Allergy and immunology in young children of Japan: The JECS cohort. World Allergy Organization Journal. 2020; 13(11). https://doi.org/10.1016/j.waojou.2020.100479 PMID: 33204389

5. Miyazaki C, Koyama M, Ota E, Swa T, Mlunde LB, Amiya RM, et al. Allergic diseases in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis. BMC Psychiatry. 2017; 17(1):120. https://doi.org/10.1186/s12888-017-1281-7 PMID: 28359274.

6. von Stülpnagel CC, Augustin M, Düpmann L, da Silva N, Sommer R. Mapping risk factors for cumulative life course impairment in patients with chronic skin diseases—a systematic review. J Eur Acad Dermatol Venereol. 2021. Epub 2021/05/15. https://doi.org/10.1111/jdv.17348 PMID: 33988873.

7. Furue M, Kadono T. "Inflammatory skin march" in atopic dermatitis and psoriasis. Inflamm Res. 2017; 66(10):833–42. Epub 2017/06/18. https://doi.org/10.1007/s00011-017-1065-z PMID: 28620798.

8. Nomura I, Katsunuma T, Tomikawa M, Shibata A, Kawahara H, Ohya Y, et al. Hypoproteinemia in severe childhood atopic dermatitis: a serious complication. Pediatr Allergy Immunol. 2002; 13(4):287–94. Epub 2002/10/23. https://doi.org/10.1034/j.1399-3038.2002.01041.x PMID: 12390445.

9. Shoda T, Futamura M, Yang L, Yamamoto-Hanada K, Narita M, Saito H, et al. Timing of eczema onset and risk of food allergy at 3 years of age: A hospital-based prospective birth cohort study. J Dermatol Sci. 2016; 84(2):144–8. https://doi.org/10.1016/j.jdermsci.2016.08.003 PMID: 27523805.

10. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health. 2014; 14:25. https://doi.org/10.1186/1471-2458-14-25 PMID: 24410977.

11. Yamamoto-Hanada K, Ishitsuka K, Pak K, Saito M, Ayabe T, Mezawa H, et al. Allergy and mental health among pregnant women in the Japan Environment and Children's Study. J Allergy Clin Immunol Pract. 2018; 6(4):1421–4 e2. https://doi.org/10.1016/j.jaip.2017.12.006 PMID: 29366732.

12. Yamamoto-Hanada K, Pak K, Saito-Abe M, Sato M, Ohya Y. Better maternal quality of life in pregnancy yields better offspring respiratory outcomes: A birth cohort. Ann Allergy Asthma Immunol. 2021; 126 (6):713–21.e1. Epub 2021/02/28. https://doi.org/10.1016/j.anai.2021.02.019 PMID: 33639261.

13. Programme Office of Japan Environment and Children's Study NIfES. Japan Environment and Children's Study (JECS) Study Protocol. https://www.env.go.jp/chemi/ceh/en/about/advanced/material/jecs-study_protocol_14_en.pdf.

14. Programme Office of Japan Environment and Children's Study NIfES. Japan Environment and Children's Study (JECS) Sub-Cohort Study Protocol. https://www.env.go.jp/chemi/ceh/en/about/advanced/material/jecs-sub-cohort_study_protocol_101-en.pdf.

15. Cole TJ. The LMS method for constructing normalized growth standards. Eur J Clin Nutr. 1990; 44 (1):45–60. Epub 1990/01/01. PMID: 2354692.

16. Kato N, Takimoto H, Sudo N. The Cubic Functions for Spline Smoothed L, S and M Values for BMI Reference Data of Japanese Children. Clin Pediatr Endocrinol. 2011; 20(2):47–9. Epub 2011/04/01. https://doi.org/10.1297/cpe.20.47 PMID: 23926394.

17. Isojima T, Kato N, Ito Y, Kanzaki S, Murata M. Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. Clin Pediatr Endocrinol. 2016; 25(2):71–6. Epub 2016/05/24. https://doi.org/10.1297/cpe.25.71 PMID: 27212799.

18. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. J Am Acad Dermatol. 2015; 72(4):606–16.e4. Epub 2015/03/17. https://doi.org/10.1016/j.jaad.2014.12.013 PMID: 25773409.

19. Johansson EK, Ivert LU, Bradley B, Lundqvist M, Bradley M. Weight gain in patients with severe atopic dermatitis treated with dupilumab: a cohort study. BMC Dermatol. 2020; 20(1):8. Epub 2020/09/24. https://doi.org/10.1186/s12895-020-00103-0 PMID: 32962676.

20. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. Clin Exp Allergy. 2015; 45(1):255–64. Epub 2014/09/12. https://doi.org/10.1111/cea.12406 PMID: 25210971.

21. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. J Invest Dermatol. 2017; 137 (1):18–25. Epub 2016/10/25. https://doi.org/10.1016/j.jid.2016.08.022 PMID: 27771048.