A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics

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Background: Previous studies found conflicting results about the commonality of different atopic dermatitis (AD) signs and symptoms.

Objective: To determine the prevalences of AD characteristics and differences by region and age.

Methods: A systematic review was performed of all published studies in MEDLINE, EMBASE, SCOPUS, LILACS, Cochrane, China National Knowledge Infrastructure, Taiwan Electronic Periodical Services, and CiNii that analyzed the proportion of AD characteristics. Two reviewers performed a review study titles and/or abstracts and data abstraction.

Results: In all, 101 studies reported proportion of AD features with sufficient data for meta-analysis. The most prevalent AD features were pruritus, lichenification, and xerosis. There were differences in AD characteristics by study region. Flexural involvement was less commonly reported in India, the Americas, and Iran. Studies from East Asian reported more erythroderma and truncal, extensor, scalp, and auricular involvement. Studies from Southeast Asia reported more exudative eczema, truncal involvement, lichenification, and prurigo nodularis. Studies from Iran reported more head, face, and neck involvement; pityriasis alba; and xerosis. Studies from Africa reported more papular lichenoid lesions, palmar hyperlinearity, ichthyosis, and orbital darkening.

Limitations: Heterogeneity between studies and limited reporting of certain AD clinical characteristics.

Conclusions: AD characteristics are heterogeneous and vary by region and age. (J Am Acad Dermatol 2019;80:390-401.)

Key words: atopic dermatitis; diagnostic criteria; eczema; epidemiology; meta-analysis; phenotype; prevalence; signs; symptoms; systematic review.

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Dr Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Dr Silverberg and Dr Yew were responsible for the study concept and design. Dr Yew was responsible for acquisition of data. Dr Silverberg, Dr Yew, and Dr Thyssen were responsible for analysis and interpretation of data, as well as for drafting of the article and critical revision of the article for important intellectual content. Dr Yew was responsible for statistical analysis, and Dr Silverberg obtained funding for the study.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease with significant patient and population burden,[1] affecting 5% to 20% of children and 2% to 10% of adults worldwide.[2-5] The prevalence and incidence of AD vary widely between different geographic regions[3] owing to different underlying genetics and environmental factors.

Patients with AD display different clinical presentations depending on age,[6-8] ethnicity,[9] and the underlying biologic mechanisms.[10] To properly diagnose AD, clinicians should be cognizant of phenotypic differences. Previous studies have found conflicting results about the commonality of different AD signs and symptoms across regions and ages. In this study, we evaluated, quantified, and compared the prevalence of AD characteristics across regions and ages.

CAPSULE SUMMARY

- This study identified considerable heterogeneity of atopic dermatitis, with 78 different signs and symptoms identified, as well as notable differences by study region and age group.
- These phenotypic differences should be incorporated into the diagnosis and severity assessment of patients with atopic dermatitis.

METHODS

Literature search

A systematic review and meta-analysis of all studies that evaluated the prevalences of clinical features of AD in various populations was planned a priori. The following databases were searched for articles up to February 15, 2018: Medline (1910-2018), Embase (1973-2018), Scopus (1908-2018), LILACS (1981-2018), Cochrane (2004-2018), China National Knowledge Infrastructure (1984-2018), Taiwan Electronic Periodical Services (1969-2018) and CiNii (a Japanese database maintained by the National Institute of Informatics, Japan) (1961-2018). The search strategy was modified from a previous Cochrane review of AD[11] to also include a number of search terms related to AD phenotypes (Table I).

The inclusion criteria were cross-sectional, case-control, or cohort study design; analysis and sufficient reporting of the prevalence of clinical features of AD; outpatient or general population; article in any language; and article published online, in print, or in press. Clinical trials were excluded. Title and abstract review was performed independently by 2 reviewers, with conflicts resolved by discussion. Additional studies were identified from manual searches of references in retrieved articles. Foreign language articles in East Asian languages (Chinese, Japanese, and/or Korean) were interpreted by study team members proficient in these languages. Articles in European languages were translated with Google Translate. If data were duplicated in multiple studies, the most recent and complete study was included. This study was exempt from institutional review board approval, as data were gathered from published literature.

Data extraction

Data extraction was performed by 2 reviewers and included study year, country, design, participant age range, sample size, frequency of clinical features, and method used to diagnose AD. AD features were first identified by using diagnostic criteria and then expanded by using features reported across studies. The study regions included the Americas, Europe, Australia, and Africa. Asia was subdivided into East Asia (EA) (China, Japan, and Korea), Southeast Asia (SEA) (Singapore and Thailand), India, and Iran owing to the disparate genetic backgrounds, ethnicities, and environments of residents of these regions.

Meta-analysis

Few studies provided 95% confidence intervals (CIs) for prevalence. Standard error was calculated for each study by assuming prevalence as a Bernoulli random variable (p), with variance being equal to $p(1-p)$.[12] Random-effects models of DerSimonian and Laird were used to estimate pooled prevalences of AD characteristics,[13] owing to heterogeneity between studies ($I^2 > 25\%$).[14] Prevalences and 95% CIs were presented in forest plots. Random-effects meta-regression and stratified meta-analysis were performed to compare the prevalences of features of AD by region and age group. A 2-sided P value less than .05 was considered statistically significant. Statistical analyses were performed using STATA software (version 13.0, StataCorp, College Station, TX).

RESULTS

Search results

Overall, 9208 nonduplicate citations were identified in the database search and 49 additional records were identified through references; 9050 and 28 were excluded during title/abstract and full-text review, respectively. In all, 130 studies met the inclusion/exclusion criteria and were included in the systematic review; 101 had sufficient data for

Abbreviations used:

AD: atopic dermatitis
CI: confidence interval
EA: East Asia
SEA: Southeast Asia
UKWP: United Kingdom Working Party

meta-analysis, as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[15] diagram (Fig 1). A total of 14 non-English articles were included (Chinese [n = 5], Japanese [n = 1], Korean [n = 4], German [n = 2], Italian [n = 1], and Polish [n = 1]).

Study characteristics

The 101 observational studies were published from 1984 to 2017.[7,16-116] Of these 101 studies, 39 (38.6%) were prospective cohort studies, 10 (9.9%) were retrospective cohort studies, 22 (21.8%) were case-control studies, and 30 (29.7%) were cross-sectional studies. Funding was reported in 36 studies (35.6%), with 6 (16.7%) funded federally, 18 (50.0%) funded by a foundation, 3 (8.3%) funded federally and by a foundation, 1 (2.8%) funded federally and by a hospital, 5 (13.9%) funded by a hospital, 1 (2.8%) funded by a pharmaceutical company, and 2 (5.6%) unfunded.

The 101 studies were conducted across 28 countries, including 29 (28.7%) in EA, 48 (47.5%) in Europe, 4 (4.0%) in SEA, 6 (5.9 %) in India and Iran (all Middle Eastern studies were from Iran), 8 (7.9%) in the Americas, and 7 (6.9%) in Africa and Australia. Thirty-six studies (35.6%) were performed in adults, 38 (37.6%) in children/adolescents, and 27 (26.7%) in both age groups. In total, 105 cohorts were available for meta-analysis by age group. Race/ethnicity was reported in 41 studies (40.6%), with only 4 (4.0%) reporting inclusion of any black subjects.

AD was diagnosed clinically in most studies (n = 78 [77.2%]), most commonly by using the Hanifin and Rajka diagnostic criteria (n = 44 [43.6%]), followed by the United Kingdom Working Party (UKWP) diagnostic criteria (n = 17 [16.8%]) (Table II). Diagnoses of AD was also identified by using diagnostic codes from review of health records (n = 14 [13.9%]) and questionnaire responses (n = 9 [8.9%]).

Pooled prevalence of AD features

Pooled meta-analysis of the proportion of AD features was determined by using random-effects weighting owing to heterogeneity (I^2 = 38.9%-99.0%). The most prevalent AD features were pruritus (32 studies [pooled prevalence, 94.0%; 95% CI, 93.1%-94.9%]) and xerosis (53 studies [pooled prevalence, 73.3%; 95% CI, 68.5%-78.0%]) (Fig 2). Other common clinical features included lichenification (7 studies [pooled prevalence, 65.8%; 95% CI, 37.7%-93.9%]), course influenced by emotional and/or environmental factors (7 studies [pooled prevalence, 59.6%; 95% CI, 43.9%-75.3%]), flexural involvement (44 studies [pooled prevalence, 58.2%; 95% CI, 49.4%-67.0%]), early onset of disease (20 studies [pooled prevalence, 56.8%; 95% CI, 36.0%-77.6%]), and worsening of itch with sweating (25 studies [pooled prevalence, 55.3%; 95% CI, 43.1%-

Table I. Search strategy

Ovid (Medline) (n = 4175 articles)
1. exp Dermatitis/; 2. dermatitis.ti,ab.; 3. exp Eczema/; 4. eczema.ti,ab.; 5. exp Neurodermatitis/; 6. neurodermatitis.ti,ab.; 7. exp Dermatitis, Atopic/; 8. Besnier's prurigo.mp; 9. or/1-8; 10. Phenotyp*.ti,ab.; 11. Morpholog*.ti,ab.; 12. distribu*.ti,ab.; 13. or/10-12; 14. exp animals/ not humans.sh.; 15. 9 and 13 not 14
Embase (n = 3035 articles)
(phenotyp* OR morpholog* OR distribu*) AND ('atopic dermatitis'/exp OR 'atopic dermatitis' OR 'eczema'/exp OR 'eczema' OR 'childhood'/exp OR childhood AND ('eczema'/exp OR eczema) OR 'infant'/exp OR infant AND ('eczema'/exp OR eczema) OR 'neurodermatitis'/exp OR 'neurodermatitis' OR 'prurigo'/exp OR 'prurigo')
Cochrane
1. exp Dermatitis/; 2. dermatitis.ti,ab.; 3. exp Eczema/; 4. eczema.ti,ab.; 5. exp Neurodermatitis/; 6. neurodermatitis.ti,ab.; 7. exp Dermatitis, Atopic/; 8. Besnier's prurigo.mp; 9. or/1-8; 10. Phenotyp*.ti,ab.; 11. Morpholog*.ti,ab.; 12. distribu*.ti,ab.; 13. or/10-12; 14. exp animals/ not humans.sh.; 15. 9 and 13 not 14
Scopus (n = 3508 articles)
(TITLE-ABS-KEY ("dermatitis") OR TITLE-ABS-KEY ("eczema") OR TITLE-ABS-KEY ("neurodermatitis") OR TITLE-ABS-KEY ("atopic dermatitis")) AND (TITLE-ABS ("phenotyp*") OR TITLE-ABS ("morpholog*") OR TITLE-ABS ("distribu*")) AND NOT (animals OR rabbits OR rats OR primates OR dogs OR cats OR swine OR "in vitro")
LILACS (n = 151 articles)
(TW:dermatitis OR TW:eczema OR TW:neurodermatitis OR TW: "atopic dermatitis") AND (TW:phenotyp$ OR TW:morpholog$ OR TW:distribu$) AND NOT (MH:animals OR MH:rabbits OR MH:rats OR MH:primates OR MH:dogs OR MH:cats OR MH:swine OR PT:"in vitro")
CNKI (n = 5564 articles)
(KY = "湿疹" OR KY = "特应性皮炎" OR KY = "儿童湿疹" OR KY = "婴儿湿疹" OR KY = "神经性皮炎 "OR KY = "痒疹") AND FT = "特征"+"分布"+"症状"
Taiwan Electronic Periodical Services (n = 549 articles)
[ALL]:湿疹 OR [ALL]:特應性皮炎 OR [ALL]:兒童濕疹 OR [ALL]:嬰兒濕疹 OR [ALL]:神經性皮炎 OR [ALL]:癢疹

CNKI, Chinese National Knowledge Infrastructure.

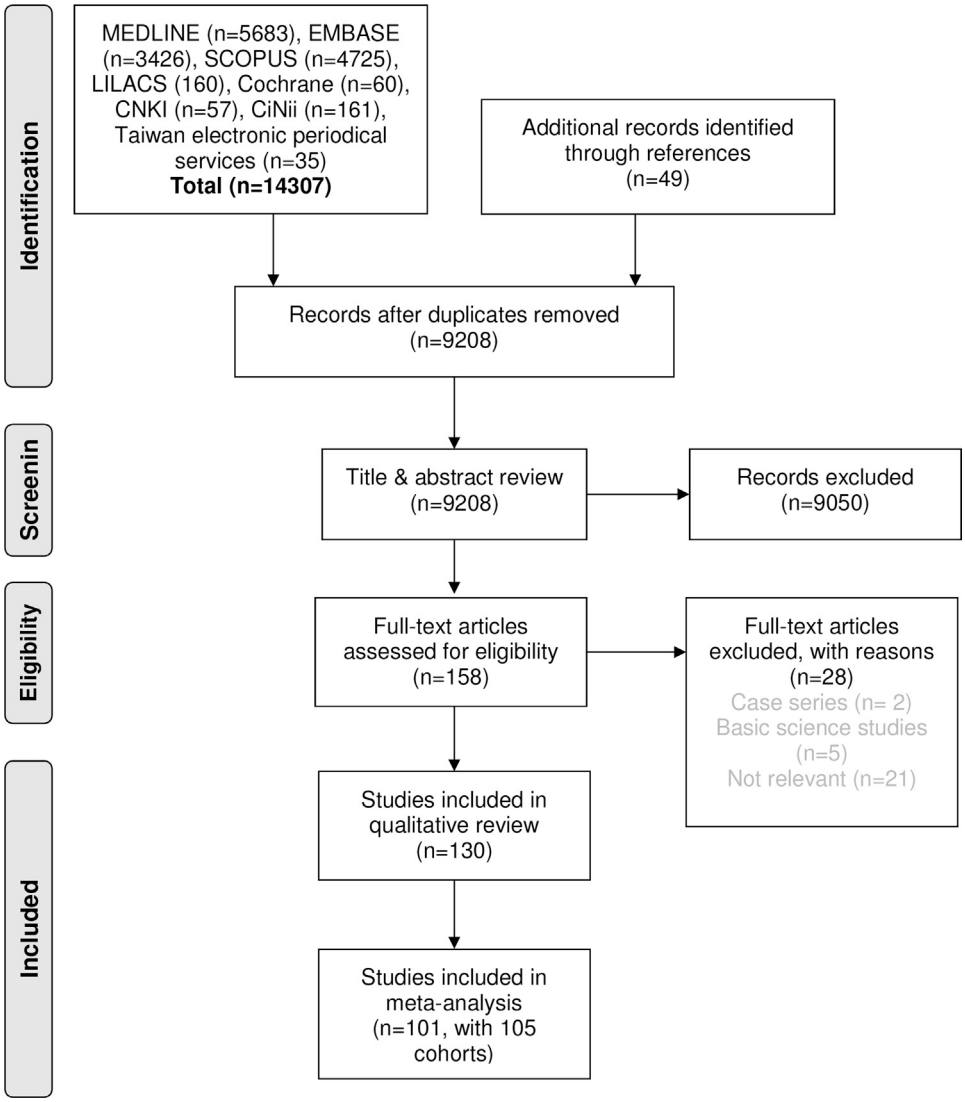

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

67.6%]). Interestingly, diaper dermatitis was reported in a substantial minority of pediatric patients (5 studies [pooled prevalence, 12.8%; 95% CI, 7.2%-18.3%]).

Regional differences in AD characteristics

Xerosis was among the top 5 most commonly reported AD features in all regions, except SEA (62.3% [95% CI, 54.9%-69.7%]). Pruritus was reported in more than 90% of subjects in studies from EA, SEA, the Americas, and Australia, though it was not reported in India.

There were notable differences in AD features by study region. Flexural involvement was reported most commonly in Australia, followed by in Africa, SEA, EA, India, and Europe, and less commonly in the Americas and Iran. Extensor involvement was most commonly reported in India, followed by in EA and Iran. Head, face, and neck involvement was reported most commonly in Iran, Africa, and the Americas, followed by in Australia, EA, Europe, and India, and least commonly in SEA. Dennie-Morgan fold was reported most commonly in India, followed by in Europe and Africa and less commonly in Iran, the Americas, SEA, and EA.

Early-onset disease was reported most commonly in SEA and India, but to a lesser extent in Europe and EA. Interestingly, itch was reported to worsen with sweating similarly in SEA, the Americas, EA, Europe, and India, but to a lesser extent in Africa and least commonly in Iran.

The most commonly reported AD features also included immediate skin reactivity in the Americas and SEA; recurrent conjunctivitis in the Americas; exudative eczema in SEA; pityriasis alba and palmar hyperlinearity in Iran; and orbital darkening, papular

Table II. Regional differences in diagnostic criteria used in studies

Region	Country	Frequency of studies	Diagnostic criteria							Diagnostic codes/clinic records	Self-reported/ questionnaire
			H-R	UKWP	JDA	Millennium	KDC	Other	Not specified		
The Americas (n = 8)	United States	6	2							3	1
	Mexico	1	1								
	Colombia	1						1			
East Asia (n = 29)	China	11	7	2				1	1		
	Japan	10	2	1	1			1	1	3	1
	Korea	8	6				1		1		
Southeast Asia (n = 4)	Singapore	1		1							
	Thailand	3	2	1							
India (n = 4)	India	4	4								
Middle East (n = 2)	Iran	2		2							
Europe (n = 48)	Bosnia	1	1								
	Denmark	7	1	4							2
	Finland	1								1	
	France	1		1							
	Germany	7	2					2		2	1
	Italy	6	4	1					1		
	The Netherlands	1				1					
	Norway	1	1								
	Poland	3	3								
	Romania	1		1							
	Sweden	11	3	1					1	3	3
	Switzerland	3						2		1	
	Turkey	2	2								
	United Kingdom	2	1							1	
	Multiple sites	1									1
Africa (n = 4)	Nigeria	2	1						1		
	South Africa	1		1							
	Tunisia	1	1								
Australia (n = 2)	Australia	2		1					1		
Total (%)		101	44 (43.6)	17 (16.8)	1 (1.0)	1 (1.0)	1 (1.0)	7 (6.9)	7 (6.9)	14 (13.9)	9 (8.9)

H-R, Hanifin and Rajka criteria; *JDA*, Japanese Dermatological Association; *KDC*, Korean Diagnostic Criteria; *UKWP*, United Kingdom Working Party.

Rank	Clinical Features	Overall (%)	Region								Age group		
			East Asia (n=29)	India (n=4)	SEA (n=4)	Africa (n=4)	America (n=8)	Australia (n=2)	Iran (n=2)	Europe (n=48)	Children (n=38)	Adults (n=36)	Unspecified (n=27)
1	Pruritus	94%	98%	.	100%	77%	100%	94%	70%	86%	92%	95%	89%
2	Cold extremities	73%	.	73%	.	.	.	.	.	.	73%	.	.
3	Xerosis	73%	72%	81%	62%	65%	82%	81%	64%	76%	73%	72%	75%
4	Lichenification	66%	.	46%	100%	.	20%	.	.	75%	48%	100%	57%
5	Course influenced by emotions/environmental	60%	74%	26%	50%	.	88%	.	.	59%	32%	72%	73%
6	Flexural involvement	58%	63%	59%	64%	65%	54%	82%	10%	58%	58%	62%	48%
7	Early onset disease	57%	42%	80%	83%	9%	.	.	5%	60%	57%	62%	42%
8	Immediate skin test reactivity	56%	12%	.	85%	.	94%	.	.	54%	52%	59%	.
9	Itch worse when sweating	55%	65%	51%	75%	39%	68%	.	2%	53%	49%	65%	43%
10	Perleche	54%	.	.	.	.	.	.	.	57%	.	57%	41%
11	Personal/Family hx of atopy	53%	56%	74%	68%	4%	60%	76%	24%	54%	50%	60%	49%
12	Raised Total Ig E	52%	54%	.	41%	.	.	.	.	53%	57%	51%	46%
13	Extensor involvment (Upper limbs)	51%	53%		78%	.	.	.	46%	19%	52%	51%	.
14	Exudative eczema	50%	32%	.	100%	.	.	.	.	43%	61%	42%	.
15	Course influenced by environment	48%	71%	35%	75%	20%	46%	.	7%	44%	37%	62%	61%
16	Upper limb involvement	47%	51%	.	34%	57%	62%	9%	.	49%	56%	38%	60%
17	intolerance to wool and lipid solvents	45%	41%	42%	24%	11%	.	.	6%	56%	45%	47%	37%
18	Dennie-Morgan infraorbital fold	42%	18%	78%	22%	49%	27%	.	33%	50%	47%	36%	40%
19	Head, face, neck involvement	42%	49%	37%	16%	61%	58%	48%	72%	35%	38%	39%	60%
20	Low Hair Line	42%	.	69%	.		.		14%	.	42%	.	.
21	Auricular rhagades	41%	34%	.	.	.	.	.	.	43%	42%	39%	41%
22	Cradle cap (scaling and crusting of the scalp during	40%	43%	.	.	.	.	39%	.	39%	41%	39%	.
23	Lower limb involvement	40%	47%	.	39%	51%	57%	9%	.	38%	48%	32%	48%
24	Peeling skin at proximal nailfold	39%	.	39%	.	.	.	.	.	.	39%	.	.
25	Trunk involvement	39%	60%	.	58%	.	34%	.	6%	27%	40%	40%	26%
26	Ichthyosis/palmar hyperlinearity/keratosis pilaris	38%	34%	.	.	.	50%	.	.	37%	25%	44%	.
27	Infra-auricular fissuring	38%	54%	10%	10%	8%	.	.	.	40%	34%	56%	27%
28	Trunk and Limbs	38%	38%	.	.	.	.	.	.	.	38%	.	.
29	Non-specific hand or foot dermatitis	36%	29%	18%	37%	20%	43%	16%	.	42%	25%	44%	35%
30	Palmar hyperlinearity	36%	32%	40%	49%	52%	.	.	32%	37%	35%	39%	33%
31	Orbital darkening	35%	32%	32%	52%	54%	.	.	9%	37%	32%	38%	37%
32	White dermographism/delayed blanch	35%	28%	43%	10%	7%	4%	.	8%	50%	34%	34%	38%
33	Perifollicular accentuation	34%	43%	35%	27%	.	5%	.	5%	28%	37%	21%	54%
34	Scalp eczema	34%	40%	42%	16%	.	52%	.	9%	15%	33%	29%	50%
35	Allergic shiner	32%	32%	.	.	.	.	.	.	.	.	32%	.
36	Anterior neck folds/involvement	32%	29%	23%	50%	.	51%	.	.	32%	34%	35%	21%
37	Blepharal involvement	31%	37%	.	29%	.	44%	22%	.	25%	40%	28%	32%
38	Course influenced by emotions	30%	.	18%	2%	.	72%	.	.	32%	15%	70%	
39	Food intolerance	29%	21%	7%	29%	.	24%	.	15%	38%	28%	28%	42%
40	Cheilitis	28%	30%	11%	8%	4%	28%	7%	3%	42%	23%	31%	28%
41	Auricular involvement	27%	32%	.	24%	.	31%	23%	.	12%	28%	25%	30%
42	Keratosis pilaris	27%	21%	33%	9%	17%	.	.	18%	36%	25%	28%	28%
43	Urticaria	27%	23%	.	.	.	.	.	.	33%	20%	32%	.
44	Cutaneous infections	26%	20%	36%	12%	.	26%	.	.	32%	25%	21%	56%
45	Ventral wrist dermatitis	26%	26%	.	13%	13%	58%	.	.	24%	34%	15%	32%
46	Extensor involvment (lower limbs)	25%	34%	.	.	.	.	.	.	15%	24%	25%	.
47	Insect bite reaction	25%	.	42%	.	.	.	.	.	9%	42%	.	9%
48	Seborrheic dermatitis like	25%	39%	.	19%	.	.	.	.	24%	40%	18%	2%
49	Pityriasis alba	23%	20%	44%	21%	13%	8%	.	46%	23%	28%	18%	21%
50	Recurrent conjunctivitis	23%	16%	9%	15%	.	88%	.	.	25%	22%	21%	50%
51	Forehead lichenification	22%	30%	.	.	11%	.	.	.	19%	24%	17%	22%
52	Papular lichenoid lesions	22%	12%	.	.	54%	.	.	1%	46%	8%	46%	32%
53	Photophobia	22%	8%	.	.	.	.	.	.	27%	.	26%	11%
54	Infra-auricular/nasal fissuring	21%	21%	.	.	.	.	.	.	.	21%	.	.
55	Ichthyosis	19%	22%	8%	15%	21%	.	.	.	9%	16%	18%	23%
56	Infragluteal dermatitis	18%	18%	.	.	.	.	.	.	.	18%	17%	21%
57	Sign of Hertoghe	16%	15%	.	1%	.	.	.	8%	24%	2%	25%	19%
58	Dyshidrosis / pomphylox	14%	13%	.	3%	.	4%	.	.	24%	3%	21%	10%
59	Knuckle dermatitis of hands	14%	10%	.	.	4%	.	.	.	31%	8%	25%	6%
60	Diaper rash	13%	5%	.	.	.	.	13%	.	17%	13%	13%	.
61	Keratolysis exfoliativa	13%	13%	.	.	.	.	.	.	.	13%	13%	13%
62	Nummular plaques	13%	16%	.	21%	.	6%	.	6%	11%	10%	18%	8%
63	Acrocyanosis	12%	.	.	.	.	.	.	31%	12%	.	12%	.
64	Dirty neck	11%	11%	.	14%	.	.	.	.	10%	10%	11%	13%
65	Erythroderma	11%	41%	.	.	.	.	34%	3%	1%	1%	29%	.
66	Nail involvement (pitting, shiny, hangnail, leuconych	11%	7%	.	.	20%	16%	.	6%	23%	8%	15%	12%
67	Nipple eczema	11%	11%	5%	11%	8%	11%	.	.	14%	8%	15%	9%
68	Fine hair	9%	.	9%	.	.	.	.	.	.	9%	.	.
69	Fissured heels	8%	11%	.	.	5%	.	.	.	.	8%	12%	7%
70	Palmar erythema	8%	7%	.	.	9%	.	.	.	.	.	6%	8%
71	Genitalia involvement	7%	9%	.	5%	.	.	6%	2%	7%	7%	7%	8%
72	Prurigo nodules	7%	8%	.	27%	.	.	.	4%	4%	4%	18%	2%
73	Anterior subcapsular cataracts	5%	2%	.	.	.	8%	.	.	6%	0%	6%	12%
74	Geographical tongue	3%	2%	.	6%	.	.	.	.	.	5%	2%	2%
75	Pitted keratolysis	3%	4%	.	.	2%	.	.	.	.	6%	4%	3%
76	Infra-nasal fissuring	1%	1%	.	.	.	.	.	.	.	1%	.	.
77	Keratoconus	1%	3%	.	.	.	0%	.	.	0%	4%	1%	1%
78	Lichen amyloidosis	1%	1%	.	.	.	.	.	.	.	.	1%	.

Fig 2. Random-effects proportions of clinical characteristics occurring in atopic dermatitis overall and stratified by different regions and ages are presented using a color-coded heat map (dark green indicates 0% and dark red indicates 100%).

lichenoid lesions, and palmar hyperlinearity in Africa.

Differences in features compared with those in studies from Europe

Compared with European studies, studies from EA reported higher prevalences of erythroderma and truncal, extensor, scalp, and auricular involvement but lower prevalences of immediate skin test reactivity, Dennie-Morgan infraorbital fold, personal/family history of atopy, or white dermographism. Studies from SEA reported higher prevalences of exudative eczema, immediate skin test reactivity, truncal involvement, lichenification, and prurigo nodularis, but lower prevalences of white dermographism, Dennie-Morgan infraorbital folds, cheilitis, and intolerance to wool and lipid solvents than in European study participants. Iranian studies reported higher prevalences of head, face, and neck involvement; pityriasis alba; and xerosis; however, they reported lower prevalences of worsening of itch with sweating, flexural involvement, and intolerance to wool or lipid solvents. African studies reported higher prevalences of papular lichenoid lesions, palmar hyperlinearity, ichthyosis and orbital darkening, but lower prevalences of personal/family history of atopy, white dermographism. and cheilitis.

In meta-regression, significant differences were found for pruritus (P = .016), keratosis pilaris (P = .010), trunk (P = .001), nail involvement (P = .001), white dermographism (P = .024), and intolerance to wool and lipid solvents (P = .020) by region. Marginally significant differences were found for infra-auricular fissuring (P = .058) and forehead lichenification (P = .059).

Differences in AD features by age

Compared with adult studies, pediatric studies reported higher prevalences of dermatitis of the eyelid, auricular area, and ventral aspect of the wrist; exudative eczema; seborrheic dermatitis—like features; and early-onset disease (as defined by age of onset younger than 2 years). Conversely, adults had higher pooled prevalences of lichenification, erythroderma, disease course influenced by emotions and/or environmental factors, ichthyosis, palmar hyperlinearity, keratosis pilaris, nonspecific hand and foot dermatitis, dyshidrosis, prurigo nodularis, and papular lichenoid lesions.

In a meta-regression comparing pediatric and adult studies, the prevalences of nonspecific hand and foot dermatitis (P = .004), sign of Hertoghe (P = .040), nipple eczema (P = .038), and disease course influenced by emotions and/or the environment (P = .026) were significantly higher in adults, whereas children had significantly higher prevalences of dermatitis of the ventral aspect of the wrist (P = .041).

DISCUSSION

This systematic review and meta-analysis, which has identified 78 different clinical characteristics of AD reported internationally, highlights the heterogeneity of AD signs and symptoms. Pruritus was almost universally reported and was the most common feature, emphasizing pruritus as an essential feature in all diagnostic criteria for AD. Otherwise, xerosis, lichenification, disease course influenced by emotional and/or environmental factors, flexural involvement, and early onset of disease were the most prevalent AD features. Notably, these features are all present in the Hanifin and Rajka diagnostic criteria,[117] though disease course influenced by emotional and/or environmental factors is not present in UKWP[118] and American Academy of Dermatology[119] diagnostic criteria for AD. There were marked differences in AD characteristics by region and age. Classic flexural involvement was reported less commonly in the Americas and Iran. Extensor lesions were more commonly reported in India, EA, and Iran. Studies from EA reported more course influenced by emotional and/or environmental factors, xerosis, worsening of itch with sweating, flexural and trunk involvement, and higher proportions of erythroderma and auricular involvement. In contrast, studies from SEA reported more lichenification, exudative eczema, immediate skin test reactivity, and extensor involvement. Iranian studies reported more head, face, and neck involvement; xerosis; extensor involvement; and pityriasis alba. Yet, African studies reported more xerosis; flexural involvement; head, face, and neck involvement; upper limb involvement; orbital darkening; and papular lichenoid lesions. Taken together, there appear to be regional differences in AD phenotypes. There are myriad environmental factors that affect the prevalence and course of AD.[120] It is unknown whether these clinical differences are also related to environmental factors particular to those regions or continue when individuals relocate to other regions. These differences may have important ramifications for AD diagnostic criteria in different regions and proper clinical diagnosis of AD in patients from different regions. For example, the Japanese Dermatological Association diagnostic criteria for AD include the forehead, auricular area, and trunk as symmetric predilection sites.[121] These body sites do not appear in the Hanifin and Rajka,[117] UKWP,[118] or American Academy of Dermatology criteria.[119] These latter criteria may perform well in whites and persons of Northern European descent; however, they may not

perform well in persons of Asian, African, or Iranian descent, given the observed lower rates of at least 1 criterion in these regions (eg, flexural involvement, early-onset disease, personal/family history of atopy).

Recent studies postulated that the "Asian phenotype" of AD includes more chronic, lichenified, and psoriasiform lesions and increased cytokine production by type 1 and type 17 helper T cells.[122-124] However, Asia encompasses a huge geographic region with many different racial and ethnic groups. We found considerable heterogeneity of AD even within Asia, with phenotypic differences between EA, SEA, Iran, and India. For example, subjects from EA had more truncal involvement and extensor lesions, whereas those from SEA had more exudative lesions and lichenification. It has also been reported that facial and eyelid eczema are more common in Asians, especially in female Asians.[125] However, this systematic review revealed that head, facial, and neck lesions were less common among patients in SEA. It is imperative that future studies of the clinical and molecular AD phenotypes precisely describe subjects' origin within particular regions and ethnicity.

Regional differences in AD phenotype may reflect underlying differences in population genetics, climate, allergen, and other environmental factors, as well as behavioral differences in responses to pruritus. Filaggrin gene (*FLG*) gene null mutations lead to xerosis from a deficiency of natural moisturizing factor,[126] disruption of epidermal barrier function (allowing increased penetration of allergens and development of a type 2 helper T-cell–predominant phenotype),[127] and earlier-onset and more severe AD.[128,129] Although specific *FLG* mutations have been identified in European[130] and Asian[131] populations, they are not present in the majority of AD cases. They are also rare in South African, Ethiopian, and African American populations.[132-134] Although there are likely different genetic factors in patients of African descent with AD, it is interesting to note that palmar hyperlinearity and ichthyosis, which are the clinical hallmarks of *FLG* mutation carriers, have been frequently reported in African studies. Climate is associated with AD prevalence. Lower temperature and increased number of indoor heating days were associated with increased AD prevalence,[135,136] likely owing to increased time spent indoors with low ambient indoor humidity. In contrast, extreme heat and humidity may lead to worsening of itch in AD. Interestingly, worsening of itch with sweating was less commonly reported in studies from Africa and Iran. This may be related to the consistently hot temperatures all year long in those regions, which may obfuscate patients' appreciation of climate's impact on their AD.

Pediatric AD was associated with more exudative lesions and seborrhea-like features, whereas adults had more chronic phenotypic features (eg, lichenification, erythroderma, and hand and foot dermatitis). Clinical differences between pediatric and adult AD may be related to disease chronicity, underlying differences in cytokine profiles,[137,138] skin microbiome and barrier, and behavioral differences. More studies are needed to understand molecular and phenotypic correlations in AD. Interestingly, diaper dermatitis was reported in 1 in 8 children with AD, which is within the 7% to 35% prevalence range of diaper dermatitis previously reported.[139] AD is commonly reported to spare the diaper area.[140] However, our results suggest that diaper dermatitis commonly occurs in children with AD.

Strengths of this study include the large number of studies across various geographic regions, inclusion of non–English language articles, and comprehensive search strategy that included multinational and Asian language databases. The conglomeration of multiple studies allowed for adequate statistical power to provide fairly precise prevalence estimates of different AD characteristics and meta-regression across age groups and regions. However, there were limitations, including limited and variable reporting of certain clinical characteristics of AD. Some characteristics may have been presented but not documented or reported. It is imperative that future studies comprehensively describe the phenotype of patients with AD. The list of signs and symptoms identified in this study can be used as a guide. Few studies were performed in some regions (eg, India and the Middle East). As such, some regional differences should be interpreted with caution. We were unable to determine whether regional differences applied to native persons or other descents. Some AD features were not accounted for in the studies (eg, eyelash length[141] and lip pigmentation).[142] Future studies of AD characteristics should prospectively examine the multiple clinical features and disease phenotypes identified.

In conclusion, this study demonstrates the wide spectrum of AD signs and symptoms, as well as phenotypic differences in AD by region and age. These differences should be incorporated into the diagnosis and assessment of patients with AD and are likely due to different immune axes and environmental and genetic factors. Further correlation with therapeutic response is required.

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