

Development and validation of new diagnostic criteria for atopic dermatitis in children of China

Ruhong Cheng, MD^{1,2*}, Hui Zhang, PhD^{1,2*}, Wenkai Zong, BA^{3*}, Jianping Tang, PhD^{4*}, Xiuping Han, PhD⁵, Li Zhang, PhD⁶, Xinglian Zhang, MD⁷, Heng Gu, MD³, Ye Shu, PhD⁴, Ge Peng, MD⁵, Lisu Huang, PhD^{8,9}, Qiang Liu, MD^{7#}, Xinghua Gao, PhD^{6#}, Yifeng Guo, MD^{1,2#}, Zhirong Yao, PhD^{1,2#}

1 Department of Dermatology, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

2 Institute of Dermatology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

3 Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, China

4 Department of Dermatology, Hunan Children's Hospital, Changsha, Hunan, China

5 Department of Dermatology, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China

6 Department of Dermatology, China Medical University First Hospital, Shenyang, Liaoning, China

7 Department of Dermatology, Children's Hospital of Shanxi, Taiyuan, Shanxi, China

8 Clinical Research Center, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

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9 Department of Pediatrics, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

*The four persons contribute equally to the study.

The four persons are co-correspondence.

Correspondence: 1. Zhirong Yao, MD, Department of Dermatology, Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China; Tel.: +862125076428; Fax: +862165030840; E-mail: yaozhirong@xinhumed.com.cn; 2. Yifeng Guo, Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China. E-mail: guoyifeng@xinhumed.com.cn; 3. Xinghua Gao, Department of Dermatology, China Medical University First Hospital, Shenyang, Liaoning, China. Email: gaobarry@hotmail.com; 4. Qiang Liu, Department of Dermatology, Children's Hospital of Shanxi, Taiyuan, Shanxi, China. Email: lqwcj@163.com;

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Abstract

Background In previous epidemiological study, the prevalence of atopic dermatitis (AD) was 12.94% among children aged 1-7ys by clinical diagnosis, whereas that was 4.76% and 3.51% using U.K., and Hanifin and Rajka diagnostic criteria.

Objective We aimed to propose new diagnostic criteria for children, and evaluate its efficiency in different populations.

Methods We screened atopic features and analyzed their correlation with AD using data from a previous study. A new set of diagnostic criteria for children in China were proposed and validated in 1,031 children in outpatient clinics, and 538 children in a birth cohort survey. Clinical diagnosis and atopic feature evaluation was performed face-to-face by dermatologists specialized in AD. Three criteria were compared for diagnostic efficiency using the clinical diagnosis as the reference.

Results The new diagnostic criteria for children were based on (i) pruritus; (ii) “typical morphology and distribution” or “atypical morphology and distribution with xerosis”; and (iii) a chronic or chronically relapsing course. Compared to classical diagnostic criteria, the sensitivity of the new diagnostic criteria was significantly higher in the epidemiological survey and the clinical setting, especially obvious among mild and moderate AD. In the birth cohort, the new criteria showed similar sensitivity and specificity.

Conclusion The new criteria for children yielded higher sensitivity for the diagnosis of AD in the epidemiological survey and clinical setting, particularly for mild and moderate AD. Among the birth cohort with a complete medical history, three criteria showed similar sensitivity and specificity.

Introduction

Atopic dermatitis (AD) is a heterogeneous disease that manifests with a wide variety of clinical symptoms and signs. It is difficult to establish standard diagnostic criteria that cover the entire spectrum of AD patients. In 1980, Hanifin and Rajka (H.R.) proposed the first widely utilized diagnostic AD criteria, and since then various diagnostic tools have been developed for hospital and community settings¹. Among such tools, the U.K. criteria are more practical and have been validated worldwide in the dermatological field; however, they have wide variations in sensitivity and specificity, as well as low positive predictive value (PPV) and negative predictive value (NPV)¹. In China, AD with milder phenotype, atypical morphology and distribution of lesions, or negative atopic history are generally diagnosed as eczema instead of AD since such cases do not fulfill the H.R. or U.K. Criteria².

In our previous study, the prevalence of AD among children aged 1-7y, was 12.94%, 4.76%, and 3.51%, based on clinical diagnosis, U.K. diagnostic criteria, and H.R. diagnostic criteria, respectively³. 63.17% of AD based on clinical diagnosis cannot fulfill U.K. criteria. 43.33% of AD denied persistent itch in the past 12 months. 51.29% denied generalized skin xerosis. 89.8% of AD didn't show visible flexural eczema. Insufficient diagnoses of AD have a substantial impact on epidemiology, as well as many other aspects related to basic research, and drug development programs in this country². Considering that a nation-wide face-to-face study conducted by dermatologists specialized in AD in 12 metropolises collected detailed information on the symptoms related to AD in the child population aged 1-7y³, we sought to explore new diagnostic criteria for children in China. The new proposed diagnostic criteria were then validated in two populations, including 1,031 children aged 1-12y visiting outpatient clinics and 538 children aged

5y, participating a multilateral prospective birth cohort.

Methods

Three different studies were performed. In the first study (epidemiological study, Original study), we evaluated atopic symptoms and signs, and proposed new diagnostic criteria for Chinese children based on data from an epidemiological study in children aged 1-7y³. In the second and third studies (Validation study), we evaluated the new diagnostic criteria for Chinese children in dermatological outpatients aged 1-12y (second study, in clinical setting), and in children aged 5 from a prospective birth cohort (third study). Our studies and the associated questionnaire were approved by the Ethical Committee of Xinhua Hospital affiliated with the Shanghai Jiaotong University School of Medicine. Permissions were also obtained from school principals and local Center for Disease Control and Prevention (CDC). Signed informed consent was obtained from all participants and their guardians.

Original study

The first population included all subjects in our previous epidemiological study³, which consisted of preschool children aged 1-7 years from kindergarten, and vaccination clinics from 12 cities (Shenyang, Beijing, Dalian, Taiyuan, Nanjing, Hefei, Shanghai, Wuhan, Chengdu, Chongqing, Changsha and Shenzhen). A total of 13,998 children from 84 kindergarten classes and 40 vaccination clinics were enrolled for the development of new diagnostic criteria for Chinese children.

All dermatologists involved in the study were specialized in AD, and have been trained to diagnose AD and AD-related features. During the study, dermatologists were randomly divided into two three-man panels. Panel A was in charge of recording general information and assessing “whether he/she was/wasn’t an AD patient, as well as the severity of AD if he/she was diagnosed

AD". General information included name, sex, age, race, address and telephone number. The clinical diagnosis of AD was evaluated following the definition of AD, an inflammatory, pruritic, chronic or chronically relapsing skin disease occurring often in families with other atopic diseases. Moreover, other allergic, pruritic, or erythematous squamous dermatosis, including contact dermatitis, psoriasis, scabies, or hereditary metabolic diseases and lymphoma were excluded. Dermatologists assessed a subject by evaluating their history and performing physical examination, which usually cost less than 10 min. Finally clinician-based diagnosis (recognized as gold standard in our studies) was determined after taking symptoms, signs, seasonal fluctuation of disease, and differential diagnose into consideration. For AD patients, disease severity was determined by the average objective components of the Scoring Atopic Dermatitis (SCORAD) index⁴ given by two dermatologists in Panel A. The objective components of the SCORAD index (clinical signs and disease extent, total score 83) classified as mild (< 15), moderate (15-40), and severe (>40).

Panel B, who was blinded to the AD status assessed by Panel A, were responsible for the assessment of "whether he/she conformed to each concrete feature". Atopic features in the U.K. and H.R. diagnostic criteria, as well as other localized or morphological variants⁵⁻⁷ were investigated in all participants, excepting non-dermatological findings, four subjective features, and invasive tests in the H.R. diagnostic criteria (Table S1). It is noted that in little kids, dermatologists evaluated presence of "pruritus" by observation of scratch activity, scratching lesions (e.g. Figure 1a), and caregivers' reporting of itching, rubbing, scratching or sleeplessness. For subjects without complete medical history or presenting an ambiguous manifestation, dermatologists failed to classify some items as "yes" or "no". The features were recorded using a question mark.

In brief, each subject was examined by two junior dermatologists from Panel A and two junior dermatologists from Panel B. The consistency of the two dermatologists in the same panel was assessed by a senior dermatologist. If inconsistency was observed, the opinion of a senior dermatologist would be adopted following additional examination of the patient.

Validation study

Two additional populations were used to validate the new proposed criteria, and compare to the classical H.R. and U.K. diagnostic criteria. One population included all subjects aged 1-12y visiting outpatient clinics in the Dermatology Departments of six tertiary hospitals in five cities (including Shenyang, Nanjing, Shanghai, Shanxi and Hunan). A total of 1,031 children with or without AD were enrolled during 2017 to 2018. The other population was from the Shanghai Obesity and Allergy Birth Cohort Study, including 1,243 pairs of mothers and their newborns⁹. A total of 538 participants who were 5 years of age between June 2017 and April 2018 and agreed to continue participating this multilateral prospective birth cohort survey were enrolled in our study. They formed the second population for validation.

The procedures for general information collection, clinical diagnosis, and atopic feature investigation were performed following the same methods as in the original study. Half of the dermatologists in the validation study also participated in the original study. In the validation study, four subjective features (itch when sweating, intolerance to wool and lipid solvents, food intolerance, course influenced by environmental and/or emotional factors) were included for evaluation by dermatologists in Panel B. For subjects in clinical settings, the reasons for attending the dermatologist, as well as the final dermatological diagnosis were also recorded by dermatologists in Panel A. For children in the birth cohort study, physical examinations were also conducted by pediatricians from the Department of Ophthalmology, Stomatology, Respiration Medicine, and Nutrition⁹.

Statistical Methods

All valid data were input into EpiData 3.1 software (The EpiData Association, <http://www.epidata.dk/>, Denmark), or the Tencent application or the Questionnaire Star application for the questionnaire, and output in a Word Processing System (WPS) 2017. WPS 2017 software was used to record information on each subject, including general information, clinical diagnosis, atopic features, all items of the SCORAD scores, and analyses of whether a subject fulfilled the related criteria were recorded by function formula. Some features recorded using a question mark were recognized as “not conformed to the atopic feature” when diagnosis

based on classical criteria was calculated. The Chi-square test in the Statistical Package for Social Science 21.0 software (SPSS Inc., Chicago, IL, USA) was used to evaluate the correlation between atopic features and AD (in various age groups). A P-value <0.05 was considered to be statistically significant. Using the dermatologists' diagnoses as the gold standard, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), misclassification and error rates (ER) were calculated.

Results

Original study and new diagnostic criteria proposed for Chinese children

In the epidemiological study, 1,811 AD and 12,187 non-AD individuals were distinguished. The distributions of atopic features, age, and gender were provided for AD cases and controls. Among 1,811 AD cases, the number of mild, moderate and severe AD was 1351(74.60%), 434(23.96%), and 26 (1.44%), respectively.

Dermatologists in our study reached an agreement that the new criteria for children would be based on features collected in original study. After a serious discussion, features based on medical history were first excluded (Table S1), because they were easy to be disturbed by recall or non-response bias. It was also concluded that palmar hyperlinearity, keratosis pilaris, perifollicular accentuation, Dennie-Morgan folds, orbital darkening, anterior neck folds, facial pallor/ facial erythema, and white dermatographism are ambiguous components with poor between-observer reproductively^{1,5}, which was also verified in our original study. During the original study, investigators used question marks to record features in above features. These ambiguous or anamnestic features were rejected unanimously. All remained features were relatively easier for investigator assessment using “yes” or “no” (Table S1). They were classified as cardinal feature, typical morphology and distribution of eczema, atypical morphology and distribution of eczema, and one quantifying feature (Table S1, Table 1 and Figure 1). Chi-square test showed that each feature selected and their combined type (“typical morphology and distribution” and “atypical morphology and distribution”) were significantly associated with AD in epidemiological study. The association of “atypical morphology and distribution” with AD showed an equivalent importance for diagnosis of AD. So, all features extracted were considered to be adopted in the new diagnostic criteria (Table 1).

. In addition, we defined “typical morphology and distribution” in our criteria based on “visible flexural eczema (or eczema involving the cheeks/forehead and extensor limbs in children under 4

years of age)" in U.K. criteria and "facial and extensor involvement in infants and children" in Hanifin and Rajka criteria. The key point is to decide whether age restriction should be set for "facial and extensor involvement" in children before adolescence in "typical morphology and distribution" of new criteria. Chi-square test was used to compare the ratio of "facial and extensor involvement" in AD and non-AD population among 4-7y children. The proportion of "facial and extensor involvement" was found in 68.21% of AD and 0.14% in non-AD ($p < 0.001$), indicating that this feature can also be adopted for children of late childhood. Thus, "typical morphology and distribution" in our new criteria was primarily merged as "flexural eczema, including facial and extensor involvement in children", which was further confirmed in validation studies. Finally, the new criteria were proposed in Table 2 (further information was explained in Discussion part).

According to the new diagnostic criteria for children, we calculated the sensitivity, specificity, PPV, NPV, misclassification, and ER, compared to that of the H.R. and U.K. diagnostic criteria (Table 3). The new diagnostic criteria showed higher sensitivity with an equivalent level of specificity.

Validation study

All 1,031 children aged 1-12y were enrolled randomly. A total of 639 children were diagnosed with AD by dermatologists. Among those participants, the number of mild, moderate and severe AD was 208(32.55%), 361(56.49%), and 70(10.95%), respectively. Some mild AD cases initially visited the dermatologists for other skin problems, such as purpura, verruca plantaris, and epidermoid cysts, but were distinguished concomitant with AD. Part of moderate and severe AD patients sought treatment for recurrent AD. Among 1031 children enrolled in the study, some of them were diagnosed with other erythroderma desquamativum or pruritic disease similar to AD, such as psoriasis, scabies, tinea, impetigo, and irritant dermatitis. Compared to the classical diagnostic criteria, the new criteria for children showed a significant advantage in sensitivity, with an equivalent level of specificity in the population (Table 4) In children aged 7-12y in clinical settings, "facial and extensor involvement" was found in 39.68% of AD, significantly higher than 3.22% in non-AD subjects($p < 0.001$).

In the prospective multilateral follow-up survey, a total of 160 children were diagnosed with AD by dermatologists. Mild and moderate AD were 131 and 29 respectively (accounting for 81.88% and 18.12% respectively). No cases were severe. The new diagnostic criteria for children exhibited equivalent diagnostic efficiency to the classical criteria (Table 4). Among children aged 5, “facial and extensor involvement” was found in 63.75% of AD, significantly higher than 0.26% in non-AD children ($p < 0.001$).

We also compared the diagnostic efficiency of the new diagnostic criteria with or without the condition of “atypical morphology and distribution with xerosis” in three populations (Table S2). In three studies, the sensitivity of the diagnostic criteria including the condition of “atypical morphology and distribution with xerosis” was higher, with the specificity to be slightly lower.

The sensitivity discrepancy of three different criteria for different levels of severity was also compared. The new criteria showed significantly advantage in sensitivity among mild and moderate AD cases (Table S3), suggesting that the new diagnostic criteria for children can effectively identify milder phenotype or phenotype with atypical morphology and distributions of lesions.

Discussion

It is widely known that the classical H.R. criteria have been a template for developing other diagnostic criteria. The U.K. criteria have been used worldwide in both hospital and community settings. After much debate, it was determined that our new proposed diagnostic criteria for children would largely be based on the H.R. and U.K. criteria. In addition, localized or morphological variants⁵⁻⁷ were also taken into consideration because of their potential value in diagnosis of AD. Common and reliable features were extracted with careful exclusion of anamnestic and ambiguous descriptions, non-dermatological findings, invasive tests, and subjective items.

After statistical analysis of data in epidemiological study, features extracted were naturally adopted in the new diagnostic criteria. Pruritus was almost universally reported and was the most common feature¹⁰, which was considered an essential feature in the new diagnostic criteria for AD. Additionally, “a chronic or chronically relapsing course” was also a common major feature for AD⁸. Typical morphology and distribution were presented in 69.91% of AD and 1.54% of non-AD patients, whereas atypical morphology and distribution data were present in 41.74% of AD and 6.97% of non-AD patients. Therefore, visible lesions, either typical or atypical morphology and distribution, can be requisite for AD diagnosis. Based on data of children aged 4-7y in original study, “Typical morphology and distribution” in our new criteria was defined as “flexural eczema, including facial and extensor involvement in children” without age restriction. The association of “facial and extensor involvement” with AD in children older than 4 and before adolescence was further confirmed in validation studies. Considering that “Atypical morphology and distribution” may result in lower specificity, another important atopic feature was in demand to obtain better specificity. In the epidemiological study, 56.1% of AD cases presented with xerosis. Xerosis is an important objective feature of AD in lesional and non-lesional skin, regardless of the genetic status¹¹. As a result, “xerosis” was listed as a complementary condition for “atypical morphology and distribution”. Finally, the new criteria proposed for Chinese children included three features (Table 2).

The new proposed criteria showed significant improvement in sensitivity compared to the H.R. or U.K. criteria, with equivalent specificity, PPV, and NPV in the epidemiological study and

clinical settings (Table 3 and Table 4). One reason for the improved sensitivity is that the new criteria raise the weight of “atypical morphology and distribution”, which can be verified by data in Table S2. The sensitivity was significantly higher using the new criteria than criteria lacking “atypical morphology and distribution with xerosis”. As a result, mild and moderate AD, or AD in remission without typical morphology and distribution can fulfill the new criteria. Accordingly, Table S3 shows that the discrepancy in sensitivity among the various criteria was more obvious in diagnosing AD of mild or moderate groups. Second, it is interesting that in the prospective birth cohort, three criteria showed similar sensitivity and specificity in diagnosing AD at age 5 (Table 4). It is commonly recognized that children in the birth cohort possessed a complete medical history, especially allergic history. Moreover, compliance and attentiveness of their families were better than that in the epidemiological study and clinical setting. Therefore, a relatively higher ratio of positive reply was given to the ambiguous or anamnestic items in the H.R. and U.K. criteria, which of course lead to a higher sensitivity closer to the true value. In contrast, for children in the epidemiological study and clinical setting, question marks were more frequently given to ambiguous or anamnestic items due to incomplete medical history or weaker compliance, resulting in a relatively lower sensitivity for H.R. and U.K. diagnostic criteria. Given this, our new criteria did not adopt ambiguous or anamnestic items to avoid a false low sensitivity for populations lacking reliable medical history.

There were two limitations of our study. The first was that our clinical diagnosis was made by a one-time examination, which was likely to exclude mild or transient AD cases. In this study, if inconsistencies existed between two dermatologists in the same panel, the assessment of a third, senior dermatologist was adopted. In contrast, follow-up examinations, or examinations twice a year (e.g., summer and winter) could render the diagnosis closer to the gold standard, which is impossible to be definitely precise due to the heterogeneity of AD¹. However, it was impossible for us to achieve this level of evaluation for such a large population. Another limitation was that our new proposed diagnostic criteria were primarily designed for dermatological specialists. In the community setting, atopic features may not be easy to distinguish. Finally, validation in a larger sample of children can be performed for more extensive use.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical features extracting from Hanifin and Rajka diagnostic criteria, U.K. diagnostic

criteria, and localized or morphological variants in epidemiological study.

Table S2. Diagnostic efficiency of two editions of new diagnostic criteria for children in three studies.

Table S3. Comparison of sensitivity of various diagnostic criteria in AD of different levels of severity.

Figure 1. Typical photographs of clinical features in the new criteria. (a) Scratch on the thigh indicating pruritus; (b) flexural eczema; (c) extensor involvement in children; (d) scalp dermatitis; (e) nipple eczema; (f) non-specific foot dermatitis; (g) eczema of fingertip; (h) eyelid eczema; (i) nail and paronychia eczema; (j) vulvar eczema; (k) nummular type of eczema (flexural eczema); (l) cheilitis; (m) prurigo type; (n) infra-auricular and retroauricular fissuring; (o) pompholyx; (p) papular lichenoid variant; (q) pityriasis alba; (r) facial xerosis.

Table 1. Comparison of atopic features selected from Table S1 between AD and non-AD cases.

		AD cases		Non AD cases			
		(n=1811)		(n=12187)			
Median age		3.15 ± 1.70		3.62 ± 3.26			
Male (percent)		869 (47.98%)		5854 (48.03%)			
Variables		Yes	percent	Yes	percent	OR	P
Cardinal features	Pruritus	1544	85.26%	92	0.75%	760.25	<0.001
	chronic or chronically relapsing course	1177	64.99%	27	0.22%	836.10	<0.001
Typical morphology and distribution							
(flexural eczema, including facial and extensor involvement in children)		1266	69.91%	188	1.54%	148.26	<0.001
Typical morphology and distribution	visible flexural eczema (or eczema involving the cheeks/forehead and extensor surface of limbs in children under 4) (U.K. diagnostic criteria)	343	18.94%	9	0.07%	316.16	<0.001
	facial and extensor involvement in children ⁸ (Hanifin and Rajka criteria)	1152	63.61%	182	1.49%	115.31	<0.001
Atypical morphology and distribution		756	41.74%	849	6.97%	9.57	<0.001
Scalp dermatitis*		111	6.12%	19	0.16%	41.82	<0.001
Nipple eczema*		11	0.61%	1	0.01%	74.47	<0.001
Non-specific hand/foot dermatitis/ Atopic winter feet*		155	8.56%	16	0.13%	71.20	<0.001
Eczema of fingertip*		67	3.70%	38	0.31%	12.28	<0.001

Atypical morphology and distribution	Eyelid eczema*	126	6.96%	10	0.08%	91.06	<0.001
	nail or paronychia eczema*	144	7.95%	348	2.86%	2.94	<0.001
	vulvar eczema*	25	1.38%	2	0.02%	85.28	<0.001
	nummular type of eczema*	82	4.53%	10	0.08%	57.75	<0.001
	eczematous lesion on other part of body*	10	0.27%	0	0	-	<0.001
	Cheilitis**	79	4.36%	74	0.61%	7.47	<0.001
	Infra-auricular and retroauricular fissuring/Infranasal fissuring**	128	7.07%	22	0.18%	42.06	<0.001
	Prurigo type**	14	0.77%	5	0.04%	18.98	<0.001
	Pompholyx**	62	3.42%	21	0.17%	20.54	<0.001
	Papular lichenoid variant**	43	2.37%	33	0.27%	8.96	<0.001
One quantifying feature	Pityriasis alba**	151	8.34%	340	2.79%	3.17	<0.001
	Xerosis	1060	56.10%	1430	11.73%	10.62	<0.001

AD, atopic dermatitis;U.K. diagnostic criteria, United Kingdom diagnostic criteria;

“*” indicates “Eczematous lesion on any part of body other than flexural areas”;

“**” indicates “ Atypical eczematous lesion”.

Table 2. New Criteria proposed for diagnosis of atopic dermatitis in children.

Atopic dermatitis is diagnosed based on three essential features	
(i)	Pruritus
(ii)	“Typical morphology and distribution (flexural dermatitis)” or “Atypical morphology and distribution with xerosis”
(iii)	A chronic or chronically relapsing course
“Typical morphology and distribution (flexural dermatitis)” including facial and extensor involvement in children;	
“Atypical morphology and distribution” includes typical eczematous lesions on locations other than the flexural areas (scalp dermatitis, eyelid eczema, nipple eczema, vulvar eczema, nummular type of eczema, eczema of fingertip, non-specific hand or foot dermatitis/atopic winter feet, nail or paronychia eczema, and eczematous lesions on other part of body) and atypical eczematous lesions (pityriasis alba, cheilitis, infra-auricular and retroauricular fissuring/ infranasal fissuring, prurigo type, pompholyx, papular lichenoid variant) .	

Table 3. Diagnostic accuracy of U.K. diagnostic criteria, H.R. diagnostic criteria and new diagnostic criteria for children in epidemiological study.

Diagnostic criteria	AD prevalence	sensitivity	specificity	PPV	NPV	ER(Misclassification)
Clinician-based diagnosis	12.94% (1811/13998)					
U.K. diagnostic criteria	4.76% (667/13998)	36.28% (657/1811)	99.92% (12177/12187)	98.50% (657/667)	91.34% (12177/13331)	8.32% (1164/13998)
H.R. diagnostic criteria	3.51% (491/13998)	26.95% (488/1811)	99.97% (12184/12187)	99.39% (488/491)	90.21% (12184/13507)	9.47% (1326/13998)
New diagnostic criteria for children	9.94% (1392/13998)	74.65% (1352/1811)	99.67% (12606/12187)	97.13% (1352/1392)	96.36% (12147/12606)	3.56% (499/13998)

U.K. diagnostic criteria, United Kingdom diagnostic criteria; H.R. diagnostic criteria, Hanifin and Rajka diagnostic criteria;

AD, atopic dermatitis; PPV, positive predictive value; NPV, negative predictive value; ER, error rate.

Table 4. Diagnostic accuracy of the Hanifin and Rajka diagnostic criteria, U.K. diagnostic criteria, and new diagnostic criteria for children in clinical settings and birth cohort study.

	Diagnostic criteria	AD prevalence	sensitivity	specificity	PPV	NPV	ER (Misclassification)
In clinical settings	clinician-based diagnosis	61.98% (639/1031)					
	H.R. diagnostic criteria	33.65% (394/1031)	51.49% (370/639)	95.41% (368/392)	94.81% (370/394)	54.68% (368/637)	31.81% (328/1031)
	U.K. diagnostic criteria	38.21% (347/1031)	57.90% (329/639)	93.87% (374/392)	93.91% (329/347)	57.77% (374/684)	28.42% (293/1031)
	New diagnostic criteria for children	49.66% (512/1031)	74.80% (478/639)	91.33% (358/392)	93.36% (478/512)	68.98% (358/519)	18.91% (195/1031)
In birth cohort study	clinician-based diagnosis	29.74% (160/538)					
	H.R. diagnostic criteria	22.12% (134/538)	68.75% (112/160)	97.62% (356/378)	92.43% (112/134)	97.62% (356/404)	10.97% (59/538)
	U.K. diagnostic criteria	24.91% (119/538)	70.00% (110/160)	94.18% (369/378)	83.58% (110/119)	88.12% (369/419)	13.01% (70/538)
	New diagnostic criteria for	23.60%	72.50%	97.09%	91.34%	89.29%	10.22%

children

(127/538)

(116/160)

(367/378)

(116/127)

(367/411)

(55/538)

U.K. diagnostic criteria, United Kingdom diagnostic criteria; H.R. diagnostic criteria, Hanifin and Rajka diagnostic criteria;

AD, atopic dermatitis; PPV, positive predictive value; NPV, negative predictive value; ER, error rates.



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- 1 **Table S1.** Clinical features extracting from Hanifin and Rajka diagnostic criteria, U.K. diagnostic criteria, and localized or morphological
 2 variants in epidemiological study.

The 1980 Hanifin & Rajka diagnostic criteria of AD ⁸ Major criteria (must have 3 or more basic features)	Features screening	U.K. criteria for AD-1994 ⁸ Must have	Features screening
Pruritus	Cardinal feature	An itchy skin condition (or parental report of scratching or rubbing in a child)	The same with Cardinal feature: pruritus
Typical morphology and distribution: -Flexural lichenification or linearity in adults -Facial and extensor involvement in infants and children	Typical morphology and distribution	Plus 3 or more of the following	
Chronic or chronically relapsing dermatitis	Cardinal feature	Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4)	Typical morphology and distribution
Personal or family history of atopy	Largely based on medical history with recall bias and non-response bias, anamnestic in subjects with incomplete history	History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including cheeks in children under 10)	Largely based on medical history with recall bias and non-response bias, anamnestic in subjects with incomplete history
Plus 3 or more of minor features		A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4)	
Nipple eczema Cheilitis	Atypical morphology and distribution	A history of a general dry skin in the last year Onset under the age of 2 (not used if child is under 4)	

Pityriasis alba		Other localized or morphological variants⁵⁻⁷	
xerosis	One quantifying feature	scalp dermatitis	Atypical morphology and distribution
Early age of onset	Largely based on medical	eczema of fingertip	
Tendency towards cutaneous infections/impaired cell-mediated immunity	history with recall bias and non-response bias, anamnestic in subjects	eyelid eczema	
Tendency towards non-specific hand or foot dermatitis	with incomplete history	nail or paronychial eczema	
Ichthyosis/palmar hyperlinearity/keratosis		pompholyx	
Dennie-Morgan infraorbital fold		vulvar eczema	
Orbital darkening	poor between-observer reproductively in literature ⁸ and based on our practice	nummular eczema	
Facial pallor/facial erythema		infra-auricular and retroauricular fissuring/ infranasal fissuring	
Anterior neck folds		prurigo type	
Perifollicular accentuation		papular lichenoid variant	
White dermographism	Ambiguous description ¹ and poor between-observer in our practice	non-specific hand or foot dermatitis/atopic winter feet	
Recurrent conjunctivitis		eczematous lesions on other part of body (neck, trunk,.....)	
Keratoconus	Non-dermatological findings not done		
Anterior subcapsular cataracts			

Itch when sweating

Intolerance to wool and lipid solvents

Food intolerance

Course influenced by environmental/emotional

Subject items without
objective evidence were
not done

Immediate (type I) skin test reactivity

Elevated serum IgE

Invasive tests not done

Delayed blanch

3 AD, atopic dermatitis; U.K. diagnostic criteria, United Kingdom diagnostic criteria; IgE, Immunoglobulin E.

Table S2. Diagnostic efficiency of two editions of new diagnostic criteria for children in three studies.

Different studies	Diagnostic criteria	AD prevalence	sensitivity	specificity	PPV	NPV
Epidemiological study	clinician-based diagnosis	12.94%				
	New					
	diagnostic criteria	9.94%	74.65%	99.67%	97.13%	96.36%
	New					
In clinical settings	diagnostic criteria	9.04%	68.19%	99.75%	97.63%	95.48%
	New					
	diagnostic criteria	61.98%				
	New					
Birth cohort study	diagnostic criteria	49.66%	74.80%	91.33%	93.36%	68.98%
	New					
	diagnostic criteria	43.26%	67.76%	96.68%	97.09%	64.79%
	New					
Birth cohort study	diagnostic criteria	29.74%				
	New					
	diagnostic criteria	23.61%	72.50%	97.09%	91.34%	89.29%
	New					
Birth cohort study	diagnostic criteria	21.75%	71.88%	99.47%	98.29%	89.31%
	New					

New diagnostic criteria: Atopic dermatitis is diagnosed based on three essential features (i) pruritus; (ii)

“typical morphology and distribution” or “atypical morphology and distribution with xerosis”; (iii) a chronic or chronically relapsing course.

New diagnostic criteria #: Atopic dermatitis is diagnosed based on three essential features (i) pruritus; (ii) “typical morphology and distribution”; (iii) a chronic or chronically relapsing course.

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- 3 AD, atopic dermatitis; PPV, positive predictive value; NPV, negative predictive value.

- 1 **Table S3.** Comparison of sensitivity of various diagnostic criteria in AD of different
 2 levels of severity.

		Mild AD	Moderate AD	Severe AD
Diagnostic sensitivity of various criteria in epidemiological study	U.K. diagnostic criteria	31.90% (431/1351)	47.69% (207/434)	73.08% (19/26)
	H.R. diagnostic criteria	20.50% (277/1351)	44.70% (194/434)	76.92% (20/26)
	New diagnostic criteria for children	69.65% (941/1351)	89.17% (387/434)	92.31% (24/26)
Diagnostic sensitivity of various criteria in clinical settings	U.K. diagnostic criteria	26.44% (55/208)	69.81% (252/361)	90.00% (63/70)
	H.R. diagnostic criteria	25.00% (52/208)	60.66% (219/361)	82.86% (58/70)
	New diagnostic criteria for children	48.56% (101/208)	86.15% (311/361)	94.29% (66/70)
Diagnostic sensitivity of various criteria in birth cohort study	U.K. diagnostic criteria	63.36% (83/131)	100% (29/29)	-
	H.R. diagnostic criteria	63.36% (83/131)	93.10% (27/29)	-
	New diagnostic criteria for children	66.41% (87/131)	100% (29/29)	-

- 3 AD, atopic dermatitis; U.K. diagnostic criteria, United Kingdom diagnostic criteria;
 4 H.R. diagnostic criteria, Hanifin and Rajka diagnostic criteria;