BJD
British Journal of Dermatology

Diagnosing atopic dermatitis in infancy using established diagnostic criteria: a cohort study

K.M.A. Endre[1,2] L. Landrø,[1,2] M. LeBlanc,[3] P. Gjersvik[1,2] K.C. Lødrup Carlsen,[2,4] G. Haugen,[2,5] G. Hedlin,[6,7] C.M. Jonassen,[8,9] B. Nordlund,[6,7] K. Rudi,[9] H.O. Skjerven,[2,4] A.C. Staff,[2,5] C. Söderhäll,[6,7] R. Vettukattil[2,4] and E.M. Rehbinder[1,2]

[1]Department of Dermatology and Venerology, Oslo University Hospital, Oslo
[2]University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Oslo, Norway
[3]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo
[4]Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo
[5]Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway
[6]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[7]Department of Women´s and Children´s Health, Karolinska Institutet, Stockholm, Sweden
[8]Genetic Unit, Centre for Laboratory Medicine, Østfold Hospital Trust, Kalnes, Norway
[9]Faculty of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Ås, Norway

Summary

Background Diagnosing atopic dermatitis (AD) in infants is challenging.
Objectives To determine the incidence and persistence of eczema and AD in infants using the UK Working Party (UKWP) and Hanifin and Rajka (H&R) criteria.
Methods A cohort of 1834 infants was examined clinically at 3, 6 and 12 months of age. AD was diagnosed by UKWP (3, 6 and 12 months) and H&R (12 months) criteria. Logistic regression models were used to assess the relationship between AD and eczema.
Results Eczema was observed in 628 (34·2%) infants (n = 240, n = 359 and n = 329 at 3, 6 and 12 months, respectively), with AD diagnosed in 212 (33·7%) infants with any eczema and in 64/78 (82%) infants with eczema at all three visits. The odds of AD were lower with first presentation of eczema at 6 [odds ratio (OR) 0·33, 95% confidence interval (CI) 0·22–0·48] or 12 months (OR 0·49, 95% CI 0·32–0·74) than at 3 months, and higher in infants with eczema at three (OR 23·1, 95% CI 12·3–43·6) or two (OR 6·5, 95% CI 4·3–9·9) visits vs. one visit only. At 12 months, 156/329 (47·4%) fulfilled the UKWP and/or H&R criteria; 27 (8%) fulfilled the UKWP criteria only and 65 (20%) only the H&R criteria. Of the 129 infants who fulfilled the H&R criteria, 44 (34·1%) did not meet the itch criterion.
Conclusions Used in combination and at multiple timepoints, the UKWP and H&R criteria for AD may be useful in clinical research but may have limited value in most other clinical settings.

What is already known about this topic?

- Eczema is common in infants, while the proportion of infants with clinical eczema having atopic dermatitis (AD) is uncertain.
- Criteria-based AD in infants increases the risk of developing allergic comorbidities, and an early appearance of AD may indicate a more severe disease phenotype.
- Studies determining AD with the UK Working Party and Hanifin and Rajka criteria in the first year of life are largely lacking.

What does this study add?

- Of 34% of infants with eczema, one-third fulfilled the diagnostic criteria for AD.

Correspondence
Kim M.A. Endre.
Email: k.m.a.s.endre@medisin.uio.no

Accepted for publication
26 January 2021

Funding sources
The PreventADALL study was funded by the following public funding bodies: Regional Health Board South East; Norwegian Research Council; Oslo University Hospital; University of Oslo, Health and Rehabilitation Norway; Foundation for Healthcare and Allergy Research in Sweden (Vårdalstiftelsen); the Swedish Asthma and Allergy Association's Research Foundation; Swedish Research Council (Initiative for Clinical Therapy Research); Swedish Heart-Lung Foundation; SFO-V Karolinska Institutet; Freemason Child House Foundation in Stockholm; Stockholm County Council (ALF-project); Østfold Hospital Trust; the European Union (MeDALL project); by unrestricted grants from the Norwegian Association of Asthma and Allergy; Kloster Foundation; Thermo Fisher Scientific; and Norwegian Society of Dermatology and Venereology, Arne Ingel's bequest.

Conflicts of interest
K.M.A.E. has received honorary for presentations from AbbVie; M.L. has received honorary for presentations from MSD; and E.M.R. has received honoraria for presentations from Sanofi Genzyme, Novartis, MEDA and Omega Pharma.

L.L. and M.L. contributed equally to this study.

DOI 10.1111/bjd.19831

- Infants with eczema at 3 months vs. later in life, or with eczema at more than one visit, were most likely to fulfil the diagnostic AD criteria.
- Except for clinical research, the present diagnostic criteria for AD may have limited clinical value in infants.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects around 20% of children in high-income countries,[1,2] and usually makes its first appearance in infancy.[3,4] The characteristics of AD, including distribution, severity, itch and persistence, vary by age group and ethnicity.[5] Although the first signs of AD often appear by 6 or 12 months of age,[6] diagnosing AD in the first year of life may be challenging, as signs of itch may be lacking and the chronicity of eczema uncertain.[7] Also, other skin conditions, for example contact dermatitis, seborrhoeic dermatitis and dermatitis associated with primary immune or nutritional deficiencies, may mimic AD.[8]

Several diagnostic criteria for AD have been developed. The Hanifin and Rajka (H&R) criteria from 1980 (revised 2003) and the H&R-derived and simplified United Kingdom Working Party (UKWP) criteria from 1994 (revised 2005) are widely used, with the UKWP criteria being most extensively validated.[9] Sensitivity and specificity vary but are generally high for both sets of criteria when applied to an adult population or children > 1 year of age.[9] However, few studies have validated the use of these diagnostic criteria in infancy.[10–12] A recent meta-analysis identified 212 randomized controlled trials, mostly including adults and older children, using 10 different diagnostic criteria for AD, with the H&R criteria the most frequently used (41%), followed by the UKWP criteria (9%).[13] The authors emphasize the need to harmonize the diagnostic criteria for AD,[13] highlighting the importance of determining the best-suited criteria for diagnosing AD in infancy.

The primary goal of this study was to determine the incidence and persistence of eczema observed at 3, 6 and 12 months of age, with a secondary goal of identifying the proportion of infants with eczema who fulfilled the UKWP and/or the H&R diagnostic criteria for AD.

Patients and methods

Design

The study was carried out within the Preventing Atopic Dermatitis and ALLergies- (PreventADALL) study, a multicentre, prospective 2 × 2 factorial interventional birth cohort study designed to investigate primary prevention strategies in AD and food allergy in infancy,[14,15] and to identify factors early in life that may be involved in the development of noncommunicable diseases.

From December 2014 to October 2016, pregnant women who consented to participate in the study at Oslo University Hospital and Østfold Hospital Trust, Norway, and at Karolinska University Hospital, Sweden, were recruited at their 18-week (between 16 and 22 + 5 weeks) routine ultrasound assessments. Exclusion criteria included inadequate skills in a Scandinavian language, plans to move away from the region shortly after birth and pregnancy with more than two fetuses. Babies of at least 35 weeks' gestational age and no severe disease were enrolled at birth. Maternal consent was obtained upon primary enrolment, with the consent of both guardians obtained shortly after birth.

Clinical follow-up visits of the infants at 3, 6 and 12 months of age included skin assessments performed by specifically trained study personnel,[15] including annual workshops, in order to minimize interobserver variability. Medical doctors with dermatological experience participated in the examinations when needed. The UKWP criteria, consisting of one major and at least three of the four minor criteria (Appendix S1; see Supporting Information) were applied at all three visits, whenever eczema was observed; the H&R criteria, requiring three of four major and three of 19 minor criteria, were additionally applied at the 12-month visit. Data on diagnosis and treatment between visits were collected by electronic questionnaires sent to infants' mothers 3, 6, 9 and 12 months after giving birth.

Baseline characteristic data were collected via electronic questionnaires at 18 and 34 weeks' gestational age. Additional information on study design, including the baseline characteristics of the 2697 mothers and 2396 babies, are reported elsewhere.[14]

The PreventADALL study is approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and Sweden (2014/2242-31/4), and is registered at ClinicalTrials.gov (NCT02449850).

Patients

Of the 2396 babies enrolled in the PreventADALL study, we included 1834 infants who attended all clinical visits at 3, 6 and 12 months of age (Figure 1). One infant was withdrawn, 223 did not attend any visit and 338 attended only one or two visits. At birth, the infants (865 girls and 969 boys) had a mean gestational age of 39·3 weeks (Table 1).

Outcomes and definitions

The main outcome was observed eczema at 3, 6 and/or 12 months of age. Eczema was defined as the presence of eczematous skin lesions verified by a physician, clinically

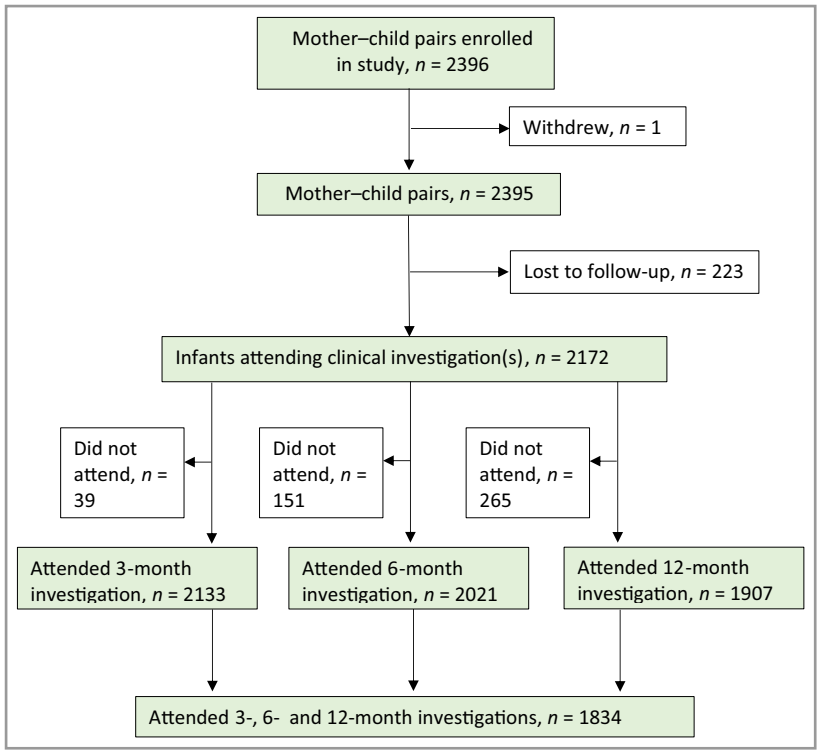

Figure 1 Enrolment of infants from the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) mother–child cohort (2701 pregnancies included).

excluding conditions with features similar to AD, for example seborrhoeic and contact dermatitis.

The secondary outcome was the proportion of children with eczema fulfilling the definition of AD by either or both the UKWP and/or the H&R diagnostic criteria at 12 months (Appendix S1). The UKWP criteria were used according to the 1994 proposed adaption of the criteria for use in infancy.[11]

Statistical analysis

Categorical variables are presented as n (%). Continuous variables are presented as mean (SD) and range. To assess selection bias, we compared the baseline characteristics for the group of PreventADALL participants included in our sample to those excluded from the present analysis, using χ^2 statistics for categorical variables and t-tests for continuous variables (Table 1). Descriptive statistics on the frequency of observed eczema in infants at the clinical visits, the use of topical steroids and a doctor's clinical diagnosis of AD between clinical visits were calculated.

Logistic regression models were used to assess the relationship between AD and eczema in infancy. As eczema is a necessary, but insufficient condition for an AD diagnosis (the probability of AD given no eczema is zero), these analyses were performed for 628 infants with eczema. A logistic regression model was used to investigate the association between one, two or three observations of eczema and the fulfilment of the diagnostic criteria by 12 months of age. A regression model was applied to examine the association between the first observation of eczema at 3, 6 or 12 months in the infants who fulfilled the diagnostic criteria. Both regression models were also adjusted for parental atopic disease and the sex of the infant.

Missing data were imputed with the best-case option, setting missing values as 0 ('no observed eczema'), assuming that parents would have been highly motivated to complete the skin examination if eczema was present. For variables concerning the use of topical steroids, missing values and 'don't know' were set to 'no use'.

All statistical analyses were performed in SPSS version 26·0 (IBM, Armonk, NY, USA). Euler diagrams were produced with eulerAPE. Bar charts were produced in GraphPad PRISM version 8·4.2 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline characteristics for the included participants attending all three follow-up visits (n = 1834) were largely similar to the nonincluded group with incomplete data (n = 594), with some exceptions. Nominally statistically significant differences included a higher level of education, income, parental age and prevalence of eczema in the included participants (Table 1).

Eczema was observed in 628 infants (34·2%) on at least one of the three clinical follow-up visits (Table 2, Figure 2a). Of the 240 infants with eczema at 3 months, 87 (36·2%) did not have eczema on further follow-up visits, while 78

Table 1 Characteristics of the study population

	Included (n = 1834)	Not included (n = 561)	Total (n = 2395)	P-value
Sex				0·74[a]
Male	969 (52·8)	292 (52·0)	1261 (52·7)	
Female	865 (47·2)	269 (48·0)	1134 (47·3)	
Nordic origin				
Mother	1531 (90·8)	432 (89·3)	1963 (90·4)	0·32[a]
Father	1484 (89·9)	419 (89·3)	1903 (89·8)	0·71[a]
Education (≥ 4 years at university)				
Mother	988 (58·8)	243 (50·4)	1231 (56·9)	0·001[a]
Father	808 (50·0)	209 (44·3)	1017 (48·7)	0·03[a]
Family income				0·005[a]
Low	214 (12·9)	88 (18·6)	302 (14·2)	
Middle	1238 (74·5)	334 (70·8)	1572 (73·7)	
High	210 (12·6)	50 (10·6)	260 (12·2)	
≥ 1 previous parity	661 (39·2)	203 (41·9)	864 (39·8)	0·27[a]
AD	186 (10·1)	15 (4·4)	201 (9·3)	0·001[a]
Eczema	628 (34·2)	57 (10·2)	685 (36·2)	0·000[a]
Eczema on two visits	222 (12·1)	NA	222 (12·1)	NA
Eczema all visits	78 (4·3)	NA	78 (4·3)	NA
Eczema present at 3 months	240 (13·1)	22 (7·4)	262 (12·3)	0·005[a]
Eczema present at 6 months	359 (19·6)	31 (16·6)	390 (19·3)	0·32[a]
Eczema present at 12 months	329 (17·9)	15 (20·5)	344 (18·0)	0·57[a]
Observed possible AD later diagnosed as AD				0·012[a]
3 months	39 (2·1)	4 (1·2)	43 (2·0)	
6 months	69 (3·8)	8 (2·4)	77 (3·5)	
9 months	9 (0·5)	1 (0·3)	10 (0·5)	
12 months	69 (3·8)	2 (0·6)	71 (3·3)	
Parental allergic disease (any)				
Mother	697 (42·2)	204 (43·4)	901 (42·5)	0·65[a]
Father	607 (35·8)	144 (31·2)	751 (34·8)	0·07[a]
AD				
Mother	333 (19·7)	98 (20·2)	431 (19·9)	0·81[a]
Father	176 (10·4)	44 (9·5)	220 (10·2)	0·60[a]
Asthma				
Mother	279 (16·5)	92 (19·0)	371 (17·1)	0·20[a]
Father	213 (12·6)	66 (14·3)	279 (12·9)	0·32[a]
Allergic rhinitis				
Mother	343 (21·2)	102 (22·3)	445 (21·5)	0·63[a]
Father	412 (24·3)	98 (21·3)	510 (23·6)	0·17[a]
Food allergy				
Mother	217 (13·2)	64 (13·6)	281 (13·1)	0·83[a]
Father	152 (9·0)	45 (9·8)	197 (9·1)	0·60[a]
Lifestyle during pregnancy				
Alcohol intake	110 (7·4)	19 (4·9)	129 (6·9)	0·09[a]
Smoking	73 (4·0)	31 (5·9)	104 (4·5)	0·07[a]
Rural living	113 (6·7)	45 (9·3)	158 (7·3)	0·052[a]
Caesarean section				
Elective	102 (6·3)	39 (7·9)	141 (6·6)	0·21[a]
Acute	192 (11·1)	60 (11·6)	252 (11·3)	0·77[a]
Born in winter	970 (52·9)	280 (49·9)	1250 (52·2)	0·22[a]
Mean (SD) gestational age at birth (weeks)	39·3 (1·7)	39·2 (1·7)	39·2 (1·7)	0·41[b]
Mean (SD) birthweight (kg)	3·6 (0·5)	3·6 (0·5)	3·6 (0·5)	0·74[b]
Mean (SD) BMI of the mother (kg m^{-2})	24·8 (3·6)	24·8 (3·9)	24·8 (3·7)	0·79[b]
Mean (SD) age of the mother (years)	32·6 (4·1)	31·7 (4·3)	32·4 (4·1)	0.0[b]
Mean (SD) age of the father (years)	34·9 (5·3)	34·1 (5·9)	34·7 (5·5)	0·01[b]
3-month investigation				
Mean (SD) age (days)	92·9 (7·9)	94·4 (8·9)	93·1 (8·1)	0·03[b]
Mean (SD) length (cm)	61·8 (2·3)	62·1 (2·7)	61·8 (2·3)	0·09[b]
Mean (SD) weight (kg)	6·2 (0·8)	6·3 (0·8)	6·3 (0·8)	0·16[b]

(continued)

Table 1 (continued)

	Included (n = 1834)	Not included (n = 561)	Total (n = 2395)	P-value
6-month investigation				
Mean (SD) age (days)	189·7 (13·3)	191·6 (14·8)	190·0 (13·5)	0·06[b]
Mean (SD) length (cm)	68·5 (2·6)	68·7 (3·1)	68·6 (2·6)	0·39[b]
Mean (SD) weight (kg)	8·1 (1·0)	8·2 (1·1)	8·1 (1·0)	0·25[b]
12-month investigation				
Mean (SD) age (days)	381·3 (23·2)	379·9 (24·6)	381·2 (23·2)	0·63[b]
Mean (SD) length (cm)	76·5 (2·9)	76·3 (3·2)	76·5 (2·9)	0·57[b]
Mean (SD) weight (kg)	10·1 (1·1)	10·0 (1·2)	10·1 (1·1)	0·56[b]

Data are n (%) unless otherwise indicated. All percentages are calculated based on the total number of responses for each variable. AD, atopic dermatitis; BMI, body mass index; NA, not applicable. [a]P-value from χ^2 statistics comparing groups with complete and incomplete data; [b]P-value from two-tailed t-test comparing groups with complete and incomplete data.

(32·5%) had eczema at all three visits (Table 2, Figure 2a). Eczema was first observed at 6 months in 236 infants (12·9%) and at 12 months in 152 (8·3%) (Table 2, Figure 2a).

Diagnostic criteria for AD by 12 months of age were fulfilled for at least one of the two validated tools in 212 (33·7%) of the infants with eczema. AD was most often diagnosed in infants with eczema at 3 months of age (n = 113; 47·1%) (Table 2, Figure 3) or with eczema at all three visits (82%; Table 2). Correspondingly, any diagnostic criteria were fulfilled by only 22% and 30% of infants with eczema first observed at 6 and 12 months, respectively (Table 2, Figure 3).

The odds of criteria-based AD by 12 months of age were significantly lower with eczema first observed at 6 months [odds ratio (OR) 0·33, 95% confidence interval (CI) 0·22–0·48; P < 0·001] and 12 months (OR 0·49, 95% CI 0·32–0·74; P = 0·001) compared with 3 months (Table 3); this was still significant after adjusting for parental atopy and infant sex (Table S1; see Supporting Information). AD was more often diagnosed in infants with eczema at three (OR

Table 2 Number of infants, n (%), with eczema fulfilling the UK Working Party (UKWP) and/or Hanifin and Rajka (H&R) diagnostic criteria for atopic dermatitis at 3, 6 and/or 12 months of age

	Total (n = 1834)	UKWP 3 months	UKWP 6 months	UKWP 12 months	H&R 12 months	UKWP infancy	UKWP/ H&R infancy
Eczema at 3 months	240 (13·1)	37 (15·4)	63 (26·2)	51 (21·2)	63 (26·2)	96 (40)	113 (47)
Eczema at 3 months only	87 (4·7)	5 (5·7)	0	0	0	5 (6)	5 (6)
Eczema at 6 months	359 (19·6)	28 (7·8)	91 (25·3)	59 (16·4)	83 (23·1)	119 (33)	143 (40)
Eczema at 6 months only	167 (9·1)	0	16 (9·6)	0	0	16 (10)	16 (10)
Eczema at 12 months	329 (17·9)	22 (6·7)	54 (16·4)	91 (27·6)	129 (39·2)	113 (34)	165 (50)
Eczema at 12 months only	152 (8·3)	0	0	22 (14·5)	35 (23·0)	22 (14)	46 (30)
Eczema at 3 and 12 months	108 (5·9)	22 (20·3)	41 (38·0)	51 (47·2)	63 (58·3)	65 (60)	82 (76)
Eczema at 3 and 12 months only	30 (1·6)	4 (13·3)	0	11 (36·7)	11 (36·7)	14 (47)	18 (60)
Eczema at 3 and 6 months	123 (6·7)	28 (22·8)	63 (51·2)	40 (32·5)	52 (42·3)	77 (63)	90 (73)
Eczema at 3 and 6 months only	45 (2·4)	10 (22·2)	22 (48·9)	0	0	26 (58)	26 (58)
Eczema at 6 and 12 months	147 (8·0)	18 (12·2)	53 (36·0)	59 (40·1)	83 (56·5)	77 (52)	101 (69)
Eczema at 6 and 12 months only	69 (3·8)	0	12 (17·4)	19 (27·5)	31 (44·9)	26 (38)	37 (54)
Eczema at 3, 6 and 12 months	78 (4·2)	18 (23·1)	41 (52·6)	40 (51·3)	52 (66·7)	51 (65)	64 (82)
Eczema on at least one visit	628 (34·2)	37 (5·9)	92 (14·6)	91 (14·5)	129 (20·5)	160 (25)	212 (34)
Eczema at only one visit	406 (22·1)	5 (1·2)	16 (3.9)	22 (5.4)	35 (8·6)	43 (11)	67 (17)

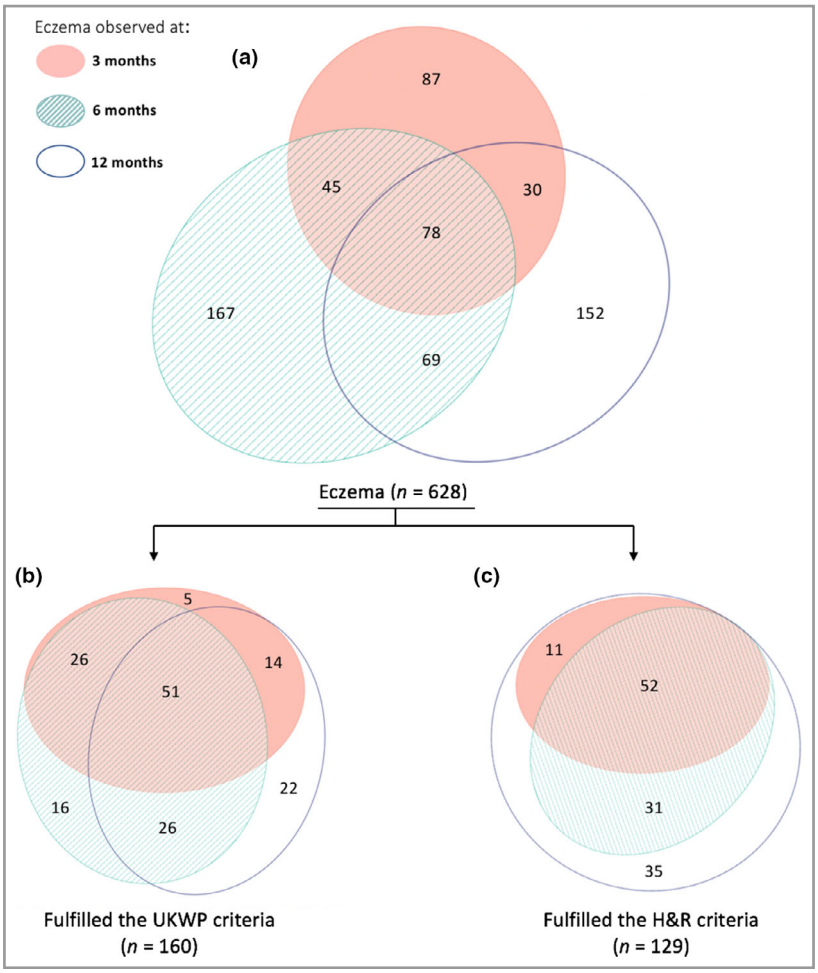

Figure 2 Area proportional Euler diagrams depicting the proportion of infants with observed eczema at the 3-, 6- and/or 12-month clinical visits in (a) the 628 infants with observed eczema in infancy; (b) the 160 infants who fulfilled the UK Working Party (UKWP) criteria; and (c) the 129 infants who fulfilled the Hanifin and Rajka (H&R) criteria (applied at 12 months only).

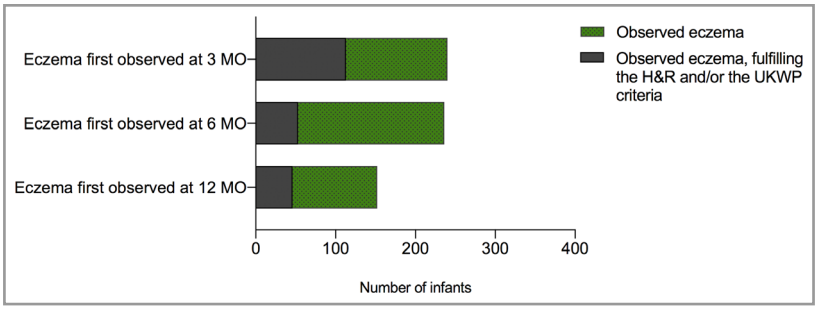

Figure 3 First observation of eczema at 3, 6 or 12 months of age in 628 infants. The grey areas illustrate those who fulfilled the UK Working Party (UKWP) and/or the Hanifin and Rajka (H&R) diagnostic criteria for atopic dermatitis by 12 months of age, while the green areas illustrate those who did not meet the criteria. The H&R criteria were applied at 12 months only.

23·1, 95% CI 12·3–43·6) or two visits (OR 6·5; 95% CI 4·3–9·9) than at one visit only (Table 4); this was also true after adjusting for parental atopy and infant sex (Table S2; see Supporting Information).

The UKWP criteria were fulfilled in 160 of 628 infants (25·5%) with observed eczema overall, and in 15% of the 240 infants with eczema at 3 months of age (Table 2). Of the 160 infants fulfilling the UKWP criteria by 12 months of age, < 15% had eczema on one occasion only (Table 2, Figure 2b). The H&R criteria, applied exclusively at 12 months, were fulfilled in 21% of all infants with eczema and 39% of infants with eczema at 12 months (Table 2, Figure 2c).

Table 3 Logistic regression model: association between first observation of eczema and fulfilling the diagnostic criteria for atopic dermatitis (UK Working Party and/or the Hanifin and Rajka criteria) in 628 infants with at least one observation of eczema in infancy

	Eczema first observed at 3 months		Eczema first observed at 6 months		Eczema first observed at 12 months	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Fulfilling the AD criteria	–	Ref.	< 0·001	0·33 (0·22–0·48)	0·001	0·49 (0·32–0·74)

Eczema at 3 months was set as the indicator. CI, confidence interval; OR, odds ratio; Ref., reference.

Table 4 Logistic regression model: number of times eczema was seen in 628 infants with at least one observation of eczema in infancy

	Eczema observed at one of three visits		Eczema observed at two of three visits		Eczema observed at three of three visits	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Fulfilling the AD criteria	–	Ref.	< 0·001	6·5 (4·3–9·9)	< 0·001	23·1 (12·3–43·6)

Eczema observed in one of three visits was set as indicator. AD, atopic dermatitis; CI, confidence interval; OR, odds ratio; Ref., reference group.

At 12 months of age, 156 of 329 infants with eczema were diagnosed with AD, with 65 fulfilling the H&R criteria only, 27 fulfilling the UKWP criteria only and 64 fulfilling both (Table 2). Additionally, nine infants with eczema at 12 months had fulfilled the UKWP criteria prior to, but not at, 12 months. The mandatory major criteria of an itchy skin condition in the UKWP criteria was reported in 85 of 129 (65·9%) infants fulfilling the H&R criteria (Table S3; see Supporting Information).

The use of topical steroids was highest in infants with eczema at all three visits (96%) vs. one visit only (52%), and in infants with eczema who fulfilled the AD criteria (79%) vs. those who did not (48%) (Table S4 and Figure S1; see Supporting Information).

Discussion

In this large, prospective, general population-based birth cohort study, clinical eczema was observed in about one-third of 1834 infants at 3, 6 and/or 12 months of age. Of these, about one-third were diagnosed with AD based on the UKWP and/or H&R diagnostic criteria for AD. Infants with eczema at 3 months of age, as well as eczema observed on three separate visits, were more likely to meet the AD criteria by 12 months of age than infants with eczema observed first after 3 months or at fewer observations. More than two in five infants with AD at 12 months fulfilled the H&R criteria only, while fewer than one in five fulfilled the UKWP criteria only.

The incidence of approximately one in three children having clinical eczema in our study is in line with a 2013 study of nearly 5000 Australian infants, where a similar proportion developed clinical eczema by 12 months of age.[16] The 12% incidence rate of AD found in our study corresponds to an estimated prevalence of AD of 20%,[2] and to the finding that 60% of German infants presented their first AD symptoms by 12 months of age.[6] However, comparing the incidence and prevalence of eczema and AD across studies is challenging, especially in infants, as the outcome definitions vary greatly. Rather than using the term 'eczema' synonymously with AD, we defined AD as fulfilling the UKWP and/or H&R diagnostic criteria.

Our finding that approximately one-third of infants with clinical eczema were diagnosed with AD adds new information about the incidence of criteria-based AD in infancy and provides a pragmatic perspective in the debate on what should be considered as AD in the first year of life. Challenges related to early diagnosis of AD in children with eczema resembles the challenges of diagnosing asthma in infants who wheeze as a result of lower respiratory tract infections.[17,18] Diagnoses of both AD and asthma are largely based on clinical signs and symptoms that are typical, but not exclusive, for the diseases.

The likelihood of AD in our study was increased in infants with observed eczema at 3 months vs. infants with a first observation of eczema at 6 or 12 months of age. This agrees with the early onset of AD being associated with an increased risk of a more severe AD phenotype.[19–21] Early fulfilment of diagnostic AD criteria may also be important in the risk of developing allergic comorbidities. In a study of > 3000 infants in Canada, meeting the UKWP criteria for AD at 12 months of age provided the best prognostic marker of all allergic outcomes at 5 years of age vs. a clinically based or a parentally reported diagnosis of AD.[22] However, Figure 3 illustrates the low sensitivity of the UKWP and H&R criteria in infancy. Also, there may be an under-recognition of skin conditions that mimic AD, such as contact dermatitis and seborrhoeic dermatitis.

Although we found a greater risk of AD in those with eczema present at 3 months of age, no further observations of eczema in infancy were seen in approximately one-third. This may be, owing, in part, to the remitting and relapsing nature of AD, or

effective treatment. However, topical steroid treatment was reported in fewer than one of five infants with eczema exclusively at 3 months vs. more than nine of 10 infants with eczema at all three visits. This also suggests that a significant proportion of those with the earliest onset of eczema will have a mild course of disease in their first year of life.

The likelihood of being diagnosed with AD in accordance with the UKWP and/or H&R criteria increased significantly with two or three observations compared with one observation only. To the best of our knowledge, this finding has not been reported previously. More than 80% of all infants with eczema present at all three visits met at least one of the diagnostic criteria, and 96% used topical steroids. Still, several skin conditions that may mimic or coexist with AD are treated with topical steroids.

In our study, 28% of infants with observed eczema at 12 months fulfilled the UKWP criteria, while 39% met the H&R criteria for AD. The higher sensitivity for detecting AD by the H&R criteria vs. the UKWP criteria found in our study is in line with a Turkish study of 200 children aged 7–36 months, which reported sensitivities of 72% and 94% for the UKWP and H&R criteria, respectively.[10] The relatively high sensitivity for both sets of criteria in the Turkish study and others could be due, in part, to the selection of children from a paediatric allergy or dermatology clinic and/or the inclusion of older children with an established diagnosis of AD,[11,12] possibly indicating more severe AD phenotypes. Our study cohort was population based. Furthermore, the higher number of infants fulfilling the H&R criteria than the UKWP criteria may, in large part, be explained by the required major criterion of an itchy skin condition in the UKWP criteria. In our study, about one-third of infants who fulfilled the H&R criteria did so without meeting the itch criterion, thereby not fulfilling the UKWP criteria. Although itch is a hallmark of the disease, a diagnosis of AD may still be made by the H&R criteria (despite no reported or observed itch) by fulfilling the remaining three major criteria and at least three minor criteria (see Appendix S1). As the UKWP criteria correspond to four major and one minor criteria in the H&R criteria, fulfilling the major criteria but not three H&R minor criteria would result in fulfilling the UKWP criteria only. The required criterion of an itchy skin condition within the last 12 months to meet the UKWP criteria may be less prominent in infants with mild skin disease,[23,24] and under-reported by caretakers. Demonstrating itch probably requires the ability to localize targets on the skin with coordinated motor skills, which may not be developed by 3 months of age,[25] putting into question the appropriateness of the UKWP's itch criterion to diagnose AD in infants aged 3 months. Although 40% of infants with eczema at 3 months met the UKWP criteria by 12 months, only 15% did so at 3 months.

The limitations of the H&R criteria include its complexity, with several minor criteria – some of which require clinical experience or additional examinations to assess – and the combination of both present features and signs or symptoms reported on behalf of the child. Also, several of the minor criteria, for example allergy, Dennie-Morgan folds, orbital darkening and palmar hyperlinearity, may not be present at the time of AD debut in infancy.

The strengths of the present study include its prospective design and the large number of infants, enrolled from three different geographical location sites in Norway and Sweden, with clinical observations performed by trained study personnel, as well as the use of two validated diagnostic criteria for AD at three different timepoints in infancy. The investigators were masked to the randomization of the participant to the interventions.[15]

This study also has some limitations. The H&R criteria, only applied at 12 months, have consistently shown higher sensitivity than the UKWP criteria in validation studies; thus, we might have underestimated the total number of infants with criteria-based AD. The fluctuating nature of AD combined with treatment plans provided at the clinical follow-up visits may also have contributed to an underestimation of the prevalence of eczema and AD at each visit. Although we recruited from the general population, many parents had a higher education and a large proportion of them reported a history of atopic disease, perhaps motivating them to participate in the study. These aspects might influence the generalizability of our results.

In conclusion, this study documents the limitations of the UKWP and H&R criteria in diagnosing AD in the first year of life. Repeated clinical observations and applying both sets of criteria may be the most appropriate way in which to diagnose AD in infants and the most useful in clinical research. However, in most clinical situations this approach may not be feasible. This suggests that the term 'infantile eczema' may be more appropriate in some infants, postponing a diagnosis of AD until the typical characteristics have been established and the diagnostic pitfalls are fewer.

Acknowledgments

We thank all the individuals involved in facilitating and running the study, including Anna Asarnoj, Karen Eline Stensby Bains, Ann Berglind, Jessica Björk, Kai-Håkon Carlsen, Oda C. Lødrup Carlsen, Ingvild Essen, Thea Aspelund Fatnes, Hrefna Katrín Gudmundsdottir, Peder Granlund, Berit Granun, Sandra Götberg, Malén Gudbrandsgard, Katarina Hilde, Mari Rønning Kjendsli, Ina Kreyberg, Caroline-Aleksi Mägi Olsson, Live Nordhagen, Carina Saunders, Natasha Sedergren, Sigrid Sjelmo, Katrine D. Sjøborg, Päivi Söderman, Sandra G. Tedner, Ellen Tegnerud, Magdalena R. Værnesbranden and Johanna Wiik.

References

1 Silverberg JI. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clin* 2017; **35**:283–9.
2 Odhiambo JA, Williams HC, Clayton TO *et al.* Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; **124**:1251–8.
3 Roduit C, Frei R, Depner M *et al.* Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatr* 2017; **171**:655–62.

4 Rudikoff D, Lebwohl M. Atopic dermatitis. *Lancet* 1998; **351**:1715–21.
5 Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. *J Am Acad Dermatol* 2019; **80**:390–401.
6 Illi S, von Mutius E, Lau S *et al.* The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; **113**:925–31.
7 Abuabara K, Margolis DJ, Langan SM. The long-term course of atopic dermatitis. *Dermatol Clin* 2017; **35**:291–7.
8 Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: mimics, overlaps, and complications. *J Clin Med* 2015; **4**:884–917.
9 Brenninkmeijer EE, Schram ME, Leeflang MM *et al.* Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol* 2008; **158**:754–65.
10 Akan A, Dibek-Misirlioglu E, Civelek E *et al.* Diagnosis of atopic dermatitis in children: comparison of the Hanifin-Rajka and the United Kingdom Working Party criteria. *Allergol Immunopathol (Madr)* 2020; **48**:175–81.
11 Williams HC, Burney PG, Pembroke AC, Hay RJ, The UK. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**:406–16.
12 Fleming S, Bodner C, Devereux G *et al.* An application of the United Kingdom Working Party diagnostic criteria for atopic dermatitis in Scottish infants. *J Invest Dermatol* 2001; **117**:1526–30.
13 Vakharia PP, Chopra R, Silverberg JI. Systematic review of diagnostic criteria used in atopic dermatitis randomized controlled trials. *Am J Clin Dermatol* 2018; **19**:15–22.
14 Lodrup Carlsen KC, Rehbinder EM, Skjerven HO *et al.* Preventing Atopic Dermatitis and ALLergies in Children-the PreventADALL study. *Allergy* 2018; **73**:2063–70.
15 Skjerven HO, Rehbinder EM, Vettukattil R *et al.* Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2020; **395**:951–61.
16 Martin PE, Koplin JJ, Eckert JK *et al.* The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. *Clin Exp Allergy* 2013; **43**:642–51.
17 Padem N, Glick Robison R. The infant and toddler with wheezing. *Allergy Asthma Proc* 2019; **40**:393–5.
18 NICE. Asthma: diagnosis, monitoring and chronic asthma management. Available at: https://www.nice.org.uk/guidance/ng80 (last accessed 5 March 2021).
19 Wan J, Mitra N, Hoffstad OJ *et al.* Longitudinal atopic dermatitis control and persistence vary with timing of disease onset in children: a cohort study. *J Am Acad Dermatol* 2019; **81**:1292–9.
20 Bieber T, D'Erme AM, Akdis CA *et al.* Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go? *J Allergy Clin Immunol* 2017; **139**(4S):S58–64.
21 Burr ML, Dunstan FD, Hand S *et al.* The natural history of eczema from birth to adult life: a cohort study. *Br J Dermatol* 2013; **168**:1339–42.
22 Dharma C, Lefebvre DL, Tran MM *et al.* Diagnosing atopic dermatitis in infancy: questionnaire reports vs criteria-based assessment. *Paediatr Perinat Epidemiol* 2018; **32**:556–67.
23 Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. U.K. Diagnostic Criteria for Atopic Dermatitis Working Party. *Br J Dermatol* 1996; **135**:12–17.
24 Johnke H, Vach W, Norberg LA *et al.* A comparison between criteria for diagnosing atopic eczema in infants. *Br J Dermatol* 2005; **153**:352–8.
25 Leed JE, Chinn LK, Lockman JJ. Reaching to the self: the development of infants' ability to localize targets on the body. *Psychol Sci* 2019; **30**:1063–73.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Outcome definitions, UK Working Party criteria, and Hanifin and Rajka criteria.

Figure S1 Euler diagram of 1141 infants with available data from clinical visits and electronic questionnaires, illustrating proportions with observed eczema and atopic dermatitis according to the diagnostic criteria, and use of steroids in infancy.

Table S1 Adjusted logistic regression model: atopic dermatitis by UK Working Party criteria and/or Hanifin and Rajka criteria, first observation of eczema, paternal any atopy, maternal any atopy and sex of the infant.

Table S2 Adjusted logistic regression model: atopic dermatitis by UK Working Party criteria and/or the Hanifin and Rajka criteria, approximate number of times eczema observed + paternal any atopy + maternal any atopy + sex of the infant.

Table S3 The number of infants fulfilling the Hanifin and Rajka criteria, with or without fulfilling the first major criteria of pruritus/itch (reported or by visible excoriations/scratch marks at the investigation) at 12 months of age.

Table S4 Infants with eczema exclusively at various timepoints and use of topical steroids.