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Persistence of atopic dermatitis (AD): A systematic review and meta-analysis

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Background: Previous studies found conflicting results about whether childhood atopic dermatitis (AD) persists into adulthood.

Objective: We sought to determine persistence rates and clinical factors associated with prolonged AD.

Methods: A systematic review was performed in MEDLINE, EMBASE, Scopus, GREAT, LILACS, Web of Science, Academic Search Complete, and Cochrane Library. Meta-analysis was performed using Kaplan-Meier plots and random-effects proportional hazards regression.

Results: In total, 45 studies including 110,651 subjects spanning 434,992 patient-years from 15 countries were included. In pooled analysis, 80% of childhood AD did not persist by 8 years and less than 5% persisted by 20 years after diagnosis (mean $\pm$ SE: 6.1 ± 0.02 years). Children with AD that persisted already for more than 10 years (8.3 ± 0.08 years) had longer persistence than those with 3 (3.2 ± 0.02 years) or 5 (6.8 ± 0.06 years) years of persistence. Children who developed AD by age 2 years had less persistent disease ($P < .0001$). Persistence was greater in studies using patient-/caregiver-assessed versus physician-assessed outcomes, female versus male patients ($P \leq .0006$), but not in those with sensitivity to allergens ($P = .90$). Three studies found prolonged persistence with more severe AD.

Limitations: Some studies did not capture recurrences later in life.

Conclusions: Most childhood AD remitted by adulthood. However, children with already persistent disease, later onset, and/or more severe disease have increased persistence. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2016.05.028>.)

Key words: atopic dermatitis; eczema; epidemiology; persistence; prognosis.

Atopic dermatitis (AD)/eczema is a chronic inflammatory skin disease with a clinical course that varies widely between patients. Some children have disease activity that persists well into adolescence and adulthood, although most children are thought to “grow out of it.” Much of the data to support this notion originate from smaller studies and did not account for a number of clinical factors that might modify disease persistence. Recent studies suggest AD may persist more commonly than

Abbreviations used:

AD: atopic dermatitis
CI: confidence interval
HR: hazard ratio

previously recognized.¹ We sought to systematically analyze the extant literature of birth cohorts and observational studies to determine the rates of disease persistence over time. Moreover, we examined

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which clinical factors associated with AD persistence may be useful for prognostication in AD.

METHODS

Literature search

We searched the following databases through June 14, 2015: MEDLINE (1946-present), EMBASE (1947-present), Scopus (1966-present), Web of Science (1900-present), Academic Search Complete (1887-present), LILACS (1982-present), GREAT (2000-present), and the Cochrane Library (1992-present). The search strategy was based on a previous Cochrane review² with inclusion of “persisten*,” “recurren*,” “natural history,” “secular history,” “disease course,” “longitudinal,” “remission,” and “cohort” as additional search terms related to disease persistence (Table I).

Studies published online, published in print, and in press from all years were considered. All search results with titles and abstracts written in any language were eligible for inclusion. Studies were excluded based on the title, abstract, or both if there was no clear indication they investigated persistence of AD. If data were duplicated in more than 1 study, the most recent and complete study was included in the meta-analysis.

Data extraction

Two reviewers (J. P. K. and L. X. C.) independently performed data extraction from these studies and any differences were resolved by discussion. The following data items were collected: first author; year of publication; study design; how AD was diagnosed; country of study; frequency of initial AD diagnosis; age and frequency of AD at follow-up; history of hypersensitivity to 1 or more allergens; severity of AD; mean age of patients and percent of males in the study. The persistence of AD was stratified by gender, allergen hypersensitivity, and baseline AD severity where available.

Statistical analysis

Statistical analyses were performed using software (SAS, Version 9.4, SAS Institute Inc, Cary, NC).

Survival analyses using the Kaplan-Meier and Cox proportional hazards regression models were used to determine the overall persistence of AD. The time-to-event variable in all models was the time from AD diagnosis to either persistence of AD or censoring. The models accounted for both left and right censoring, ie, AD diagnosis and follow-up could

happen at any age or period of observation. For studies that presented age of AD diagnosis or persistence across a range of ages, the median of the age range was selected. Models included a random effect for the study to address potential issues of heterogeneity. In addition, models were stratified by age of AD onset, number of years of already persistent disease, self-report versus physician assessment of AD, sex, and hypersensitivity to 1 or more allergens where available. Median, mean, and SE of mean AD persistence time were estimated.

Hazard ratios (HR) (95% confidence intervals [CI]) were calculated for each strata level. A 2-sided *P* value of .05 was taken as statistically significant.

RESULTS

Literature search

The literature search yielded 9960 nonduplicate articles. After review of the titles and abstracts, 9326 were excluded; an additional 634 articles were excluded after full-text review. In total, 46 studies³⁻⁴⁸ were included in the review, of which 44 had valid frequency data that could be pooled, 7 had valid data to assess the effects of gender,^{6,23,28,31,44,45,48} 6 for allergen sensitization,^{6,17,23,36,40,45} and 3 for baseline AD severity^{17,28,40} on disease persistence. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented in Fig 1.

Study characteristics

The studies were all longitudinal with respect to persistence of AD, either retrospective (*n* = 3) or prospective (*n* = 42) data collection, included both males and females, and encompassed subjects of all ages. Published years of studies ranged from 1955 to 2015. The 45 studies included 110,651 subjects spanning 434,992 patient-years from 15 countries (Supplemental Tables I to IV; available at <http://www.jaad.org>). The age of entry into the

CAPSULE SUMMARY

- Previous studies have reported conflicting results regarding the persistence of childhood atopic dermatitis into adulthood.
- Only 1 in 5 children with atopic dermatitis had disease persistence beyond 8 years. Children with already persistent disease, later onset, and more severe disease were more likely to have disease persist into adolescence and adulthood.
- These risk factors may be useful to predict which children will have persistent atopic dermatitis.

Table I. Literature search scheme for OVID MEDLINE

1. explode DERMATITIS, ATOPIC/
2. atopic dermatitis.mp.
3. dermatitis atopic.mp.
4. explode ECZEMA/or eczema.mp
5. childhood eczema.mp.
6. infantile eczema.mp.
7. neurodermatitis.mp. or exp Neurodermatitis/
8. Besnier's prurigo.mp
9. or/1-8
10. persisten*
11. recurren*
12. natural history
13. secular history
14. disease course
15. longitudinal
16. remission
17. cohort
18. or/10-17
19. 9 and 18

*Indicate wildcard characters.

cohort, ie, the age of confirmed AD, ranged from 0.04 to 17.5 years, with a mean (SD) of 1.6 ± 1.3 years. AD was diagnosed in 87.7% of subjects by age 5 years. Duration of follow-up ranged from 0.25 to 23.0 years, with a mean (SD) of 3.9 (2.8) years. Duration of follow-up was 5 years or longer in 55.7% of studies and 10 years or longer in 20.8% of studies. All subjects had AD at baseline, of which 80,477 (72.7%) had persistent AD upon follow-up at various time points.

Overall persistence of AD

In the pooled analysis, there was a precipitous decline in the overall rates of AD persistence after 3 years of follow-up (Fig 2, A). The median duration of AD persistence was 3.0 years (mean $\pm$ SE: 6.1 ± 0.02 years). In addition, persistence rates slowly continued to decrease, such that 80% of AD did not persist by 8 years and less than 5% of AD persisted by 20 years of follow-up.

Persistence of AD significantly varied by whether patients already had persistent disease. After 3 years of persistent AD, the mean (SE) additional duration of AD persistence was only 3.2 (0.02) years (median not estimable) (Fig 2, B). In patients with 5 or 10 years of persistent AD, the additional duration of persistence increased (median: 4.0 vs 8.5 years, respectively; mean $\pm$ SE: 6.8 ± 0.06 vs 8.3 ± 0.08 years, respectively).

AD persistence by age of disease onset

Persistence of AD significantly varied by age of entry into the cohort, ie, age of first confirmed AD.

The median duration of AD persistence was 3.0 years (mean $\pm$ SE: 5.8 ± 0.03 years) for subjects who were given a diagnosis of AD at age 0 to 1 year (Fig 2, C). However, the duration of persistent AD increased for subjects with AD onset by ages 2 to 5 years (median: 8.0 years; mean $\pm$ SE: 10.5 ± 0.09 years), 6 to 11 years (median: 12.5 years; mean $\pm$ SE: 14.8 ± 0.2 years), and 12 to 17 years (median not estimable; mean $\pm$ SE: 7.5 ± 0.03 years). In proportional hazards regression models, the risk for overall disease persistence was significantly higher in children with AD onset at age 2 to 5 years (HR 2.65; 95% CI 2.54-2.75) and 12 to 17 years (HR 2.04; 95% CI 1.66-2.49) compared with age of onset at 0 to 1 years, and peaked in those with onset at age 6 to 11 years (HR 4.22; 95% CI 3.86-4.61; $P < .0001$ for all).

AD persistence by self-report

There were significant differences between studies that used self-reported versus physician-assessed measures of AD at follow-up. The duration of AD persistence was significantly higher in studies that used self-reported AD (median: 6.2 years; mean $\pm$ SE: 9.6 ± 0.06 years) compared with physician-assessed AD (median: 3.0 years; mean $\pm$ SE: 5.8 ± 0.03 years) (HR 1.65; 95% CI 1.61-1.69) (Fig 2, D).

AD persistence by gender

There were 7 studies that stratified AD persistence by subjects' gender.^{6,23,28,31,44,45,48} The duration of AD persistence was significantly higher in females (median: 9.0 years; mean $\pm$ SE: 12.7 ± 0.2 years) compared with males (median: 7.0 years; mean $\pm$ SE: 11.7 ± 0.2 years) (HR 1.15; 95% CI 1.04-1.27; $P = .006$) (Fig 2, E).

AD persistence by sensitivity to allergens

There were 6 studies that stratified AD persistence by subjects' reactivity to skin-prick testing and/or antigen-specific serum IgE.^{6,17,23,36,40,45} There was no significant difference of AD persistence between those with hypersensitivity to 1 or more allergens (median: 8.1 years; mean $\pm$ SE: 8.0 ± 0.1 years) compared with none (median: 7.0 years; mean $\pm$ SE: 7.7 ± 0.1 years) (HR 1.11; 95% CI 0.92-1.33; $P = .90$) (Fig 2, F).

Similar results were found in sensitivity analyses for age of onset, self-reported disease activity, gender, and allergen sensitivity that excluded any retrospective studies.

AD persistence by baseline AD severity

There were 3 studies that stratified AD persistence by subjects' baseline AD severity,^{17,28,40} although the inconsistent measures preclude pooling of results for meta-analysis. One study found that children with

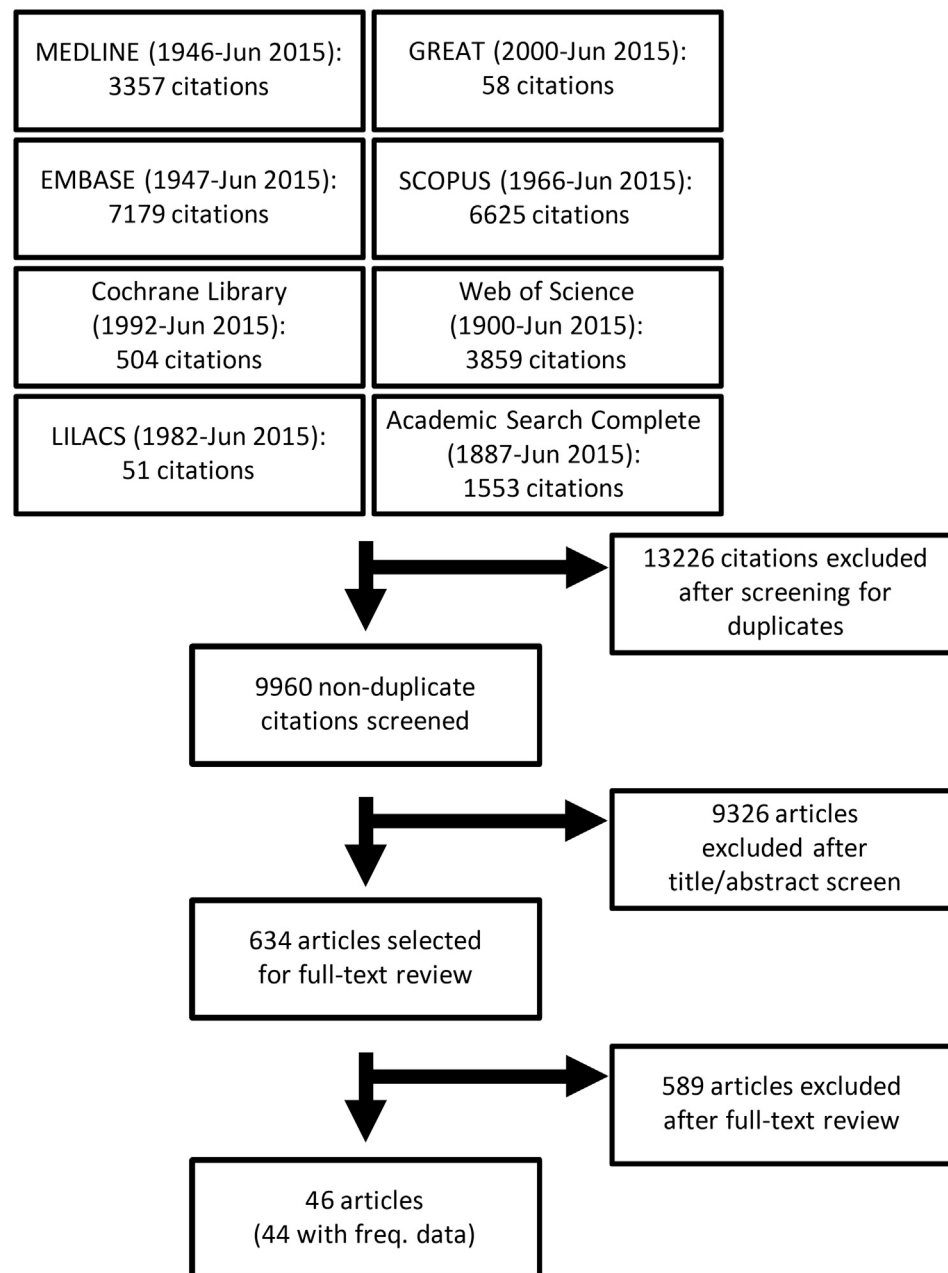


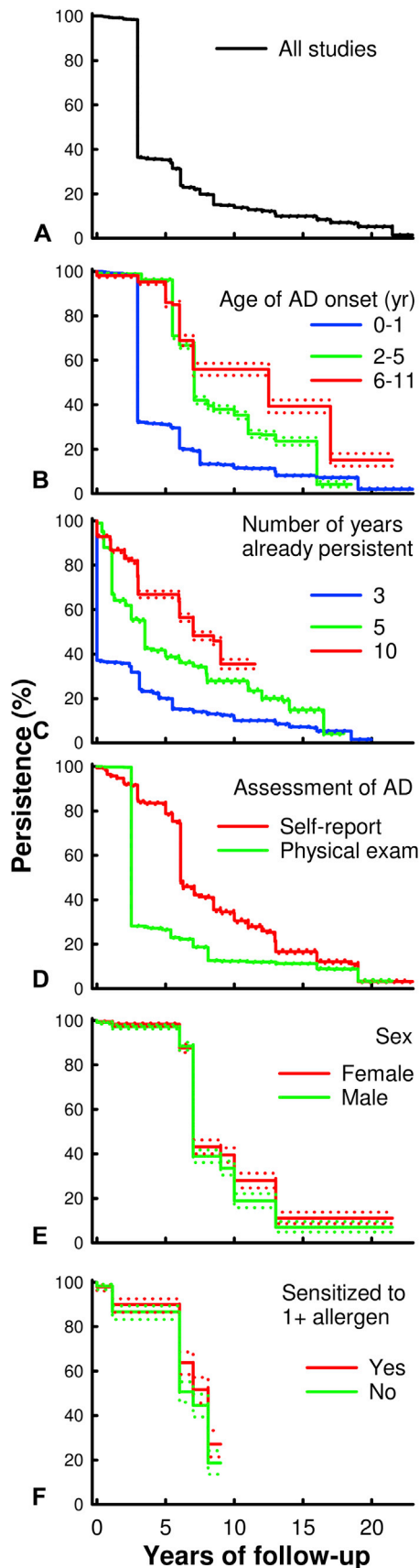
Fig 1. PRISMA flow diagram of literature search and study selection for meta-analysis of atopic dermatitis persistence.

AD onset at 0 to 2 years of age who had frequent parental-reported scratching were more likely to have persistent AD by age 7 years (81.3% vs 44.5%).¹⁷ One study found that children with AD at age 9 to 16 months who had moderate to severe compared with mild disease as judged by Scoring Atopic Dermatitis (SCORAD) were more likely to have persistent AD 6 to 12 years later (SCORAD 25-50: 51.8% and SCORAD >50: 53.8% vs SCORAD <25: 32.5%).⁴⁰ Finally, a study found that children with AD onset within the first 3 years of life who had

less than or equal to 1 or more than 1 night compared with 0 nights per week of being kept awake by their rash had higher rates of persistent AD 5 years later (52.9% and 66.7% vs 42.0%).²⁸

DISCUSSION

The results of this meta-analysis suggest that, overall, 80% of childhood AD did not persist by 8 years and less than 5% persisted by 20 years after diagnosis. Individuals with more severe disease at the time of diagnosis had increased risk for persistent



disease in 3 studies. The longer the AD already persisted, the more likely it was to continue to persist. Moreover, children who developed AD in the first 2 years of life had significantly lower risk of persistent disease than those who developed AD later in childhood or adolescence. Later onset disease might be related to exposure to irritants and contact allergens in personal care products; environmental allergens; or both. However, there were no differences of AD persistence by baseline sensitivity to 1 or more allergens. It is interesting that studies using patient-reported assessment of AD found higher risk of persistent AD compared with physician assessment. This is likely a result of the waxing and waning nature of AD, where disease activity might not be present at clinical or research visits but is present during interval periods. There was a small but significantly increased risk of persistence in females compared with males. There appeared to be more persistent disease in children with more severe AD at baseline; however, the few studies found used different severity scales that did not allow for pooled meta-analysis. Overall, the results suggest that early onset AD does tend to “burn out” and improve by adulthood. However, children with later onset, more persistent AD, and severe AD are much more likely to have prolonged persistence into adolescence and adulthood.

It is important to distinguish between AD persistence and severity. For example, even mild disease can be persistent and severe disease can spontaneously remit. The current study demonstrates that there are distinct predictors of AD persistence. We identified disease severity, older age of onset, and female gender as risk factors for persistence. Moreover, we found that cases of already persistent disease continued to persist. This suggests that the duration of AD persistence may be in a sense programmed from the disease onset. Alternatively, some environmental or behavioral risk factors for persistence may be ongoing and facilitate AD persistence. These factors may be useful for clinicians to predict which patients will have persistent AD. Long-term persistence of AD is an

Fig 2. Predictors of persistence of atopic dermatitis (AD). Kaplan-Meier survival plots and 95% log-log confidence intervals of AD persistence are presented overall (A) and stratified by age of AD onset (0-1, 2-5, 6-11 years) (B), already persistent AD (3, 5, 10 years) (C), assessment of AD (self-report, physician assessment) (D), sex (male, female) (E), and sensitization to 1 or more allergens (no, yes) (F).

important consideration for therapeutic management of AD. Patients with persistent disease often require a treatment approach that is both effective and well-tolerated over an extended period of time. Future studies are needed to develop validated tools for clinical prediction of AD persistence.

Recent studies have challenged the long-standing dogma that most childhood AD resolved by adulthood. Margolis et al¹ assessed 7157 children from the Pediatric Eczema Elective Registry, a phase IV registry of pimecrolimus users, and found that more than 80% of children had persistent disease at all ages and that only by age 20 years did 50% of patients achieve a 6-month disease-free period. The considerably higher rates of AD persistence observed in that study compared with most cohort studies were likely because of inclusion of children with more severe disease at baseline and those who already had persistent disease at enrollment. However, the results of our meta-analysis suggest that overall AD does not persist in most, when including unselected patients from birth cohorts and observational studies.

There are multiple strengths to this meta-analysis, including synthesis of a large number of international studies, including more than 100,000 patients and more than 400,000 patient-years. Kaplan-Meier and proportional hazards regression were used to account for the left and right censoring of study data. Random-effect proportional hazards models were used to address potential issues of heterogeneity. Finally, multiple sensitivity analyses were performed, which revealed important predictors of AD persistence, including age of AD onset, previous persistence of AD, baseline AD severity, and sex. We suggest that future studies stratify AD persistence by these variables to achieve more reliable estimates of AD persistence. However, this study has limitations that should be considered, including inconsistent measures of disease activity among studies. Studies were predominantly prospective with a minority being retrospective. However, there were no major differences in sensitivity analyses that excluded retrospective studies. Longer, more consistent duration of follow-up for all studies would have been preferable. There were only a few studies that stratified AD persistence by gender, sensitization to allergens, and baseline AD severity. Studies that relied on physician assessment of AD might have missed skin disease that had a more sporadic course or was clear on the day of the assessment. This is supported by our finding that AD persistence was higher in studies using self-/patient-reported assessments. Finally, we were not able to assess whether patients had AD

recurrence or flares after the observed period of remittance in the study. Thus, it is possible that some of the patients reported to have AD remittance had unobserved recurrences later in life.

In conclusion, only 1 in 5 children with AD had disease persistence beyond 8 years. However, children with already persistent disease, later onset, and more severe disease were more likely to have disease persistence into adolescence and adulthood. Future investigation into risk factors for disease persistence is warranted.

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Supplemental Table I. Study characteristics

Study	Location	Frequency with AD*		Male sex	Study design	Evaluation of AD
		Age of AD onset: frequency	Age at f/u: frequency			
Fukuzumi et al, ³ 2005	Japan	4 mo: 228	10 mo: 123	NR	Prospective cohort	Clinical examination by dermatologist
Sangsupawanich et al, ⁴ 2007	Thailand	0-6 mo: 194	12 mo: 28	49.8%	Prospective birth cohort (Prospective Cohort Study of Thai Children)	Questionnaire (recurrent rashes that look like the photograph example)
Morales et al, ⁵ 2012	Sabadell, Spain	0-6 mo: 546	7-14 mo: 513	51.9%	Prospective cohort (Infancia y Medio Ambiente Project)	Questionnaire (eczema from birth to 6 mo, from 7-14 mo)
Kawamoto et al, ⁶ 2013	Gifu, Japan	0-1 mo: 35	14 mo: 19	54.3%	Prospective cohort (Gifu Allergy and Immunology Cohort Study)	Clinical examination by allergists (Hanifin and Rajka criteria)
Perkin et al, ⁷ 2004	Avon, United Kingdom	0-1 mo: 209 0-1 mo: 209 6 mo: 320 0-1 mo: 209 6 mo: 320 18 mo: 172 0-1 mo: 209 6 mo: 320 18 mo: 172 2.5 y: 62	6 mo: 98 18 mo: 98 18 mo: 172 2.5 y: 98 2.5 y: 123 2.5 y: 62 3.5 y: 62 3.5 y: 98 3.5 y: 62 3.5 y: 25	NR	Prospective birth cohort (ALSPAC)	Questionnaire at clinic visit (based on Hanifin and Rajka criteria)

Eller et al, ⁸ 2010	Odense, Denmark	0-3 mo:	3-6 mo:	58.2%	Prospective birth cohort (DARC)	Clinical examination (Hanifin and Rajka criteria) or telephone interview with clinician
		8	4			
		0-3 mo:	6-12 mo:			
		8	4			
		0-3 mo:	12-18 mo:			
		8	4			
		3-6 mo:	6-12 mo:			
		17	14			
		3-6 mo:	12-18 mo:			
		15	9			
		6-12 mo:	12-18 mo:			
		26	14			
		0-3 mo:	1.5-3 y:			
		6	4			
		3-6 mo:	1.5-3 y:			
		14	10			
		6-12 mo:	1.5-3 y:			
		25	12			
		12-18 mo:	1.5-3 y:			
		19	7			
		0-3 mo:	5-6 y:			
		6	3			
		3-6 mo:	5-6 y:			
		14	9			
		6-12 mo:	5-6 y:			
		25	9			
		12-18 mo:	5-6 y:			
		19	11			
		1.5-3 y:	5-6 y:			
		31	14			
Matsumoto et al, ⁹ 2005	Kagawa, Japan	0-1 mo:	2 y:	NR	Prospective cohort	Clinical examination (Hanifin and Rajka criteria)
Ballardini et al, ¹⁰ 2012	Stockholm, Sweden	22	10	NR	Prospective birth cohort (BAMSE)	Questionnaire (dry skin and itchy rash in typical distribution for ≥ 2 wk or topical corticosteroid use in past 12 mo and physician diagnosis in past 24 mo)
		0-1 y:	2 y:			
		440	257			
		0-2 y:	4 y:			
		725	355			
		0-4 y:	8 y:			
		916	265			
		0-8 y:	12 y:			
		1006	245			

Continued

Supplemental Table I. Cont'd

Study	Location	Frequency with AD*		Male sex	Study design	Evaluation of AD
		Age of AD onset: frequency	Age at f/u: frequency			
Amberbir et al, ¹¹ 2011	Ethiopia	0-1 y: 72	3 y: 9	NR	Prospective birth cohort	Interviewer administered questionnaire (ISAAC)
Purvis et al, ¹² 2005	New Zealand	0-1 y: 110	3.5-4 y: 42	47.5%	Prospective case-control	1. Postal questionnaire (based on UK Working Party criteria: itchy rash in past 12 mo) 2. Clinical examination (UK Working Party criteria or visible flexural dermatitis)
Bleiker et al, ¹³ 2000	United Kingdom	1 y: 20	4 y: 11	56.2%	Prospective birth cohort	Clinical examination by dermatologist (Hanifin and Rajka and UK Working Party criteria)
Tariq et al, ¹⁴ 1998	United Kingdom	0-2 y: 122	4 y: 54	51.2%	Prospective birth cohort (1989 Isle of Wight)	Itchy, scaly, erythematous, recurrent rash with typical distribution for ≥ 6 wk
Kull et al, ¹⁵ 2006	Sweden	0-2 y: 866	4 y: 444	NR	Prospective birth cohort (BAMSE)	Questionnaire (itchy rash and dry skin with typical distribution for ≥ 2 wk in past 12 mo, physician diagnosis in past 24 mo, or both)
Ekbäck et al, ¹⁶ 2014	Sweden	0-2 y: 115 0-2 y: 94	4.5 y: 60 10 y: 60	57.8%	Prospective f/u of children with AD	Clinical examination (Hanifin and Rajka criteria)
Illi et al, ¹⁷ 2004	Germany	0-2 y: 192 0-2 y: 192 0-2 y: 192 0-2 y: 192 0-2 y: 192	3 y: 71 4 y: 65 5 y: 60 6 y: 69 7 y: 71	NR	Prospective birth cohort (German Multicenter Atopy Study)	Structured interview (physician diagnosis, parental report of AD symptoms, or visible AD at f/u)
Singh et al, ¹⁸ 2006	United States	0-1 y: 65	5 y: 30	NR	Prospective birth cohort (COAST)	NR (most likely questionnaire: AD in past 12 mo)
Gustafsson et al, ¹⁹ 2000	Sweden	0-3 y: 94 0-3 y: 94	3-5 y: 76 5-8 y: 61	NR	Prospective f/u of children with AD	Clinical examination at allergy clinic (Hanifin and Rajka criteria) and interview

van Asperen and Kemp, ²⁰ 1989	Australia	0-20 mo: 31	20 mo-5 y: 15	NR	Prospective f/u of infants with atopic parents	Clinical examination (itchy, scaly, erythematous rash with typical distribution), department of respiratory medicine and immunology
Kissling and Wüthrich, ²¹ 1993	Switzerland	0-2 y: 106 0-2 y: 106 0-2 y: 106 0-2 y: 106	2-6 y: 95 6-14 y: 87 14-20 y: 78 >20 y: 67	46.2%	Prospective f/u of children with AD	Questionnaire
Shen et al, ²² 2013	Taiwan	0-3 y: 84,956	3-6 y: 19,008	NR	Retrospective study of disease course in children with AD	Diagnostic codes from National Health Insurance Research Database
Carlsten et al, ²³ 2013	Canada	0-2 y: 62	7 y: 26	54.8%	Prospective f/u of children in a randomized controlled trial for asthma prevention	1. Clinical examination by allergist and questionnaire (ISAAC) 2. Clinical examination by same allergist (itchy rash on face or extensor surface of extremities and flexural lichenification)
Harpsøe et al, ²⁴ 2013	Denmark	0-18 mo: 5544	7 y: 2115	NR	Prospective birth cohort (Danish National Birth Cohort)	1. Telephone interview (UK Working Party criteria or Danish National Birth Cohort study diagnostic algorithm) 2. Self-administered questionnaire (ISAAC: symptoms in past 12 mo)
Burr et al, ²⁵ 2013	United Kingdom	0-1 y: OR 2.52; 95% CI 1.11-5.71 0-1 y: OR 3.61; 95% CI 1.62-8.05 7 y: OR 2.03; 95% CI 0.77-5.37 0-1 y: OR 1.95; 95% CI 0.76-5.01 7 y: OR 5.45; 95% CI 2.05-14.48 14-15 y: OR 6.04; 95% CI 2.50-14.56	7 y 15 y 15 y 23 y 23 y 23 y	50.0% (NI), 55.5% (I)	Prospective f/u of a birth cohort in a randomized controlled trial for reducing risk of allergic disease	Clinical examination
Böhme et al, ²⁶ 2012	Sweden	0-4 y: 648	8 y: 253	NR	Prospective birth cohort (BAMSE)	Questionnaire (itchy rash and dry skin with typical distribution for ≥2 wk in past 12 mo and/or physician diagnosis from age 0-4 y or since age 4 y)

Continued

Supplemental Table I. Cont'd

Study	Location	Frequency with AD*		Male sex	Study design	Evaluation of AD
		Age of AD onset: frequency	Age at f/u: frequency			
Semic-Jusufagic et al, ²⁷ 2010	United Kingdom	0-5 y: 243	8 y: 152	NR	Prospective birth cohort (Manchester Asthma and Allergy Study)	Interviewer-administered questionnaire (itchy, recurrent rash for ≥ 6 mo in past 12 mo, physician diagnosis)
von Kobyletzki et al, ²⁸ 2014	Sweden	0-1 y: 471	6 y: 249	50.5%	Prospective f/u of children with AD	Questionnaire (ISAAC: itchy, recurrent rash for ≥ 6 mo; itchy rash in past 12 mo; age rash first appeared)
		1-2 y: 320	7 y: 132			
		2-3 y: 38	8 y: 10			
		6-7 y: 51	9-10 y: 22			
Sumikawa et al, ²⁹ 2014	Japan	6-7 y: 51	9-10 y: 22	NR	Prospective cohort	Clinical examination by dermatologists (Japanese Dermatological Association criteria)
Schmitt et al, ³⁰ 2010	Germany	0-2 y: 484	10 y: 65	56.8%	Prospective f/u of a birth cohort in a randomized controlled trial for allergic disease prevention (GINIplus)	Postal questionnaire (physician diagnosis)
Hua et al, ³¹ 2014	Taiwan	0-2 y: 1404	10 y: 424	56.6%	Retrospective study of disease course in children with AD	Diagnostic codes from National Health Insurance Research Database
Kurukulaaratchy et al, ³² 2003	United Kingdom	0-1 y: 122	10 y: 50	50.8%	Prospective birth cohort (1989 Isle of Wight)	Questionnaire (ISAAC) Interviewer administered when possible, by telephone or postal otherwise
		2 y: 118	10 y: 50			
		4 y: 128	10 y: 72			
		0-1 y: 187	10-11 y: 157			
Kekki et al, ³³ 2013	Finland	0-1 y: 187	10-11 y: 157	63.1%	Prospective f/u of children with AD	1. Chart review by 2 dermatologists 2. Clinical examination

Filipiak-Pittroff et al, ³⁴ 2011	Germany	0-3 y: 188	7-10 y: 57	50.0%	Prospective f/u of a birth cohort in a randomized trial to prevent allergic diseases (GINI)	1. Clinical examination (diagnostic algorithm modified from Hanifin and Rajka criteria) 2. Questionnaire (physician diagnosis of eczema in past 4 y, treatment for eczema in past 12 mo, or both)
	Germany	0-2 y: 240	7-10 y: 49	52.1%	Prospective birth cohort (LISA)	Questionnaire 1. Physician diagnosis of allergic or atopic eczema in past 6 mo 2. Physician diagnosis of eczema during last 4 y, treatment for eczema in past 12 mo, or both
	Germany	0-2 y: 65	5-8 y: 42	62.3%	Prospective f/u of children with AD	Postal questionnaire (European Community Respiratory Health Survey, ISAAC) and clinical examination by dermatologists (UK Working Party criteria)
Williams and Strachan, ³⁵ 1998	United Kingdom	0-1 y: 368	11 y: 138	NR	Prospective birth cohort (National Child Development Study)	Structured interview 1. At age 7 y: parental report of eczematous rash at 0-1 y or after 1 y
		1-7 y: 203	11 y: 60			2. At age 11 y: parental report of eczematous rash in past 12 mo
		0-1 y: 368	16 y: 114			3. At age 16 y: parental report of eczematous rash in past 12 mo
		1-7 y: 203	16 y: 36			4. At age 23 y: self-report of eczema in past 12 mo
		10-11 y: 164	16 y: 26			
		0-1 y: 368	23 y: 107			
		1-7 y: 203	23 y: 36			
		10-11 y: 164	23 y: 27			
		15-16 y: 125	23 y: 23			
		2 y: 77	11 y: 36			
Novembre et al, ³⁶ 2001	Italy	2 y: 77	11 y: 36	NR	Prospective f/u of children with AD	Clinical examination at allergy unit (Hanifin and Rajka criteria)
Wüthrich and Schmid-Grendelmeier, ³⁷ 2002	Switzerland	2-4 y: 22	10-12 y: 15	NR	Prospective f/u of children with AEDS	Clinical examination at allergy unit of dermatology department

Continued

Supplemental Table I. Cont'd

Study	Location	Frequency with AD*		Male sex	Study design	Evaluation of AD
		Age of AD onset: frequency	Age at f/u: frequency			
Wakamori et al, ³⁸ 2009	Japan	6-7 y: 25	12-13 y: 11	NR	Prospective cohort	Clinical examination by dermatologist (UK Working Party criteria) and questionnaire (physician diagnosis, history of skin fold involvement, history of dry skin)
Vowles et al, ³⁹ 1955	United Kingdom (Bristol)	0-1 y: 78	13 y: 43	NR	Prospective f/u of children with AD	Interview of mother (closest relative for 3 cases)
Ricci et al, ⁴⁰ 2010	Italy	9-16 mo: 176	6 to 13 y: 84	55.7%	Prospective f/u of children with AD	1. Clinical examination at allergy clinic (Hanifin and Rajka criteria) 2. Telephone interview (ISAAC)
Garmhausen et al, ⁴¹ 2013	Germany	0-2 y: 248	6-14 y: 210	40.4%	Retrospective study of disease course in adolescents and adults with AD	Clinical examination and questionnaire (Hanifin and Rajka criteria, Diepgen score), department of dermatology and allergy
		2-6 y: 101	6-14 y: 87			
		0-2 y: 248	14-20 y: 216			
		2-6 y: 101	14-20 y: 91			
		6-14 y: 67	14-20 y: 58			
		0-2 y: 248	>20 y: 242			
		2-6 y: 101	>20 y: 100			
		6-14 y: 67	>20 y: 67			
		14-20 y: 79	>20 y: 77			
		0-6 y: 135	14 y: 94			
Hartwig et al, ⁴² 2014	Australia			51.9%	Prospective birth cohort (Western Australian Cohort Study)	Clinical examination and questionnaire (ever self-diagnosis or nonphysician diagnosis of eczema, ever physician diagnosis of eczema, itchy rash in skin folds)
Åberg and Engström, ⁴³ 1990	Sweden	0-2 y: 282	14 y: 164	42.7%	Cross-sectional study	Questionnaire (symptoms, age of onset, age of remission)
		2-4 y: 87	14 y: 62			
		4-7 y: 69	14 y: 41			
		7-11 y: 94	14 y: 51			

Ziyab et al, ⁴⁴ 2010	United Kingdom	0-2 y: 160 4 y: 46	10-18 y: 27 18 y: 3	52.5% 56.5%	Prospective birth cohort (1989 Isle of Wight)	Questionnaire (itchy rash in past 12 mo) Administered at f/u visit if possible, telephone or postal otherwise
Peters et al, ⁴⁵ 2010	Germany	9-11 y: 424	16-18 y: 202	NR	Prospective f/u of children age 9-11 y who participated in ISAAC phase II	Questionnaire (physician diagnosis or itchy rash with typical distribution for ≥ 6 mo in past 12 mo)
Musgrove and Morgan, ⁴⁶ 1976	United Kingdom	0-5 y: 99	15-22 y: 57	55.6%	Prospective f/u of children with AD	Clinical examination and questionnaire
Rystedt, ⁴⁷ 1985	Sweden	0-14 y: 351	≥ 24 y: 182	53.1%	Prospective f/u of children with AD	Clinical examination
Mortz et al, ⁴⁸ 2015	Denmark	0-14 y: 215 0-2 y: OR 2.0; 95% CI 1.1-3.8	28-29 y: 83 28-29 y	43.7%	Prospective cohort (f/u of the Odense Adolescence Cohort Study)	1. Questionnaire (based on Schultz-Larsen criteria) 2. Clinical examination by dermatologist (Hanifin and Rajka criteria) and questionnaire

AD, Atopic dermatitis; AEDS, Atopic Eczema Dermatitis Syndrome; ALSPAC, Avon Longitudinal Study of Parents and Children; BAMSE, Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology; CI, confidence interval; DARC, The Danish Allergy Research Centre cohort; f/u, follow-up; I, interventional cohort; ISAAC, The International Study of Asthma and Allergies in Childhood; NI, noninterventional cohort; NR, not recorded; OR, odds ratio.

*The numbers below the time points represent the number of patients with onset of AD at the time indicated, and the number of these patients evaluated at the specified follow-up.

Supplemental Table II. Persistence of atopic dermatitis stratified by sex

Study	Location	Sex	Frequency with AD*		OR (95% CI) for male sex
			Age of AD onset: frequency	Age at follow-up: frequency	
Carlsten et al, ²³ 2013	Canada	Male	0-2 y: 34	7 y: 12 (35.3%)	0.92 (0.63-1.35)
		Female	28	14 (50.0%)	
Hua et al, ³¹ 2014	Taiwan	Male	0-2 y: 794	10 y: 245 (30.9%)	
		Female	610	179 (29.3%)	
Kawamoto et al, ⁶ 2013	Gifu, Japan	Male	0-1 y: 19	14 mo: 8 (42.1%)	
		Female	16	11 (68.8%)	
Mortz et al, ⁴⁸ 2015	Denmark	Male	0-14 y: 76	28-29 y: 28 (36.8%)	
		Female	139	55 (39.6%)	
Peters et al, ⁴⁵ 2010	Germany	Total	9-11 y: 424	16-18 y: 202	
von Kobyletzki et al, ²⁸ 2014	Sweden	Male	0-3 y: 419	6-8 y: 201 (48.0%)	
		Female	410	190 (46.3%)	
Ziyab et al, ⁴⁴ 2010	United Kingdom	Male	0-2 y: 84	10-18 y: 14 (16.7%)	
		Female	76	13 (17.1%)	
		Male	4 y: 26	18 y: 0 (0.0%)	
		Female	20	3 (15.0%)	

AD, Atopic dermatitis; CAP-RAST, CAP-radioallergosorbent; CI, confidence interval; FEIA, fluorezymeimmunoassay; OR, odds ratio; SPT, skin prick test.

*The numbers below the time points represent the number of patients with onset of AD at the time indicated, and the number of these patients evaluated at the specified follow-up.

Supplemental Table III. Persistence of atopic dermatitis stratified by allergen sensitization

Study	Location	Sensitization	Frequency with AD*		OR (95% CI)	Measure of sensitization
			Age of AD onset: frequency	Age at follow-up: frequency		
Carlsten et al, ²³ 2013	Canada	No	0-2 y: 28	7 y: 10 (35.7%)		SPT on forearm epicutaneously (Bayer Inc, Toronto, Ontario, Canada): egg white, cow's milk, wheat, peanut, soy, house dust mite, cat, dog, grass, tree pollen, cockroach, <i>Alternaria alternans</i> , <i>Cladosporium herbarum</i>
		Yes	34	16 (47.1%)		
Illi et al, ¹⁷ 2004	Germany	No	0-2 y: 69	7 y: 30 (43.4%)		≥0.35 kU/L of Specific IgE to egg white, cow's milk, wheat, soy, <i>Dermatophagoides pteronyssinus</i> , cat, mixed grass, and birch pollen using CAP-RAST FEIA (Pharmacia and Upjohn, Freiburg, Germany)
		Yes	47	34 (72.3%)		
Kawamoto et al, ⁶ 2013	Japan	No	0-1 y: 10	14 mo: 2 (20.0%)		>0.34 UA/mL of Specific IgE to egg white
		Yes	24	16 (66.7%)		
Novembre et al, ³⁶ 2001	Italy	No	2 y: 28	11 y: 15 (53.6%)		SPT to egg white, milk, wheat, soy, tomato, codfish, dust mite, cat, dog, <i>Parietaria</i> , mugwort, olive pollen, and <i>Cupressus sempervirens</i> (Lofarma, Milan, Italy)
		Yes	49	21 (42.9%)		
Peters et al, ⁴⁵ 2010	Germany	No	9-11 y: 424	16-18 y: 202	1.83 (1.22-2.73)	SPT (wheal ≥3 mm after subtracting negative control) to at least 1 of the following: <i>Dermatophagoides pteronyssinus</i> , <i>Dermatophagoides</i> <i>farinae</i> , cat, <i>Alternaria tenuis</i> , mixed tree pollen, and mixed grass pollen
		Total				
Ricci et al, ⁴⁰ 2010	Italy	No	9-16 mo: 79	6-13 y: 33 (41.8%)		SPT+ to cow's milk, hen's egg, soybean, wheat, peanut, nut, codfish, apple
		Yes	97	51 (52.6%)		

AD, Atopic dermatitis; CAP-RAST, CAP-radioallergosorbent; CI, confidence interval; FEIA, fluorezymeimmunoassay; OR, odds ratio; SPT, skin prick test.

*The numbers below the time points represent the number of patients with onset of AD at the time indicated, and the number of these patients evaluated at the specified follow-up.

Supplemental Table IV. Persistence of atopic dermatitis stratified by baseline atopic dermatitis severity

Study	Location	Baseline AD severity	Frequency with AD*	
			Age of AD onset: frequency	Age at follow-up: frequency
Illi et al, ¹⁷ 2004	Germany	Frequency scratching with early AD, parental report	0-2 y:	7 y:
		No	128	57 (44.5%)
		Yes	64	52 (81.3%)
Ricci et al, ⁴⁰ 2010	Italy	SCORAD	9-16 mo:	6-13 y:
		Mild <25	40	13 (32.5%)
		Moderate 25-50	110	57 (51.8%)
		Severe >50	26	14 (53.8%)
von Kobyletzki et al, ²⁸ 2014	Sweden	No. of nights kept awake by rash	0-3 y:	6-8 y:
		None	567	238 (42.0%)
		≤1	157	83 (52.9%)
		>1	105	70 (66.7%)

AD, Atopic dermatitis.

*The numbers below the time points represent the number of patients with onset of AD at the time indicated, and the number of these patients evaluated at the specified follow-up.