A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis

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Background: Previous studies found conflicting results about whether atopic dermatitis (AD) begins in adulthood.

Objective: To determine rates, predictors, and phenotypic differences of adult-onset AD.

Methods: A systematic review was performed with all published observational studies in Medline, Embase, GREAT (Global Resource of EczemA Trials), LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Library, and Scopus that analyzed the age of AD onset beyond 10 years of age. At least two reviewers performed study title, abstract review, and data extraction. Pooled meta-analysis of the proportion of adult-onset AD was performed by using random-effects weighting (I^2 = 99.3%).

Results: Overall, 25 studies met inclusion criteria. Seventeen studies reported age of AD onset as after 16 years of age and had sufficient data for meta-analysis. The pooled proportion (95% confidence interval) of adult-onset AD was 26.1% (16.5%-37.2%). Similar results were found in sensitivity analyses by AD diagnostic method, study region, and sex. Phenotypic differences were observed across studies for adult-onset and child-onset AD, including higher rates of foot dermatitis and personal history of atopy but lower rates of flexural lesions and other signs and symptoms.

Limitations: Characteristics of adult-onset versus child-onset AD were not commonly reported.

Conclusion: AD is not only a disease of childhood; 1 in 4 adults with AD report adult-onset disease, which has distinct clinical characteristics as compared to child-onset AD. (J Am Acad Dermatol 2019;80:1526-32.)

Key words: atopic dermatitis; adult-onset; eczema; epidemiology; meta-analysis; phenotype; prevalence; systematic review.

Atopic dermatitis (AD) is a common inflammatory skin disorder affecting 13.0% of US children.[1] AD is commonly regarded as a pediatric disease. Previous studies suggested that 50% of childhood AD cases begin in the first year of life and 85% begin in the first 5 years of life.[2-4] Those studies included cohorts of children but did not assess adolescent or adult populations. In contrast, some studies of adult cohorts found high rates of AD beginning at older ages.[5]

Abbreviations used:

AD: atopic dermatitis
CI: confidence interval
SPT: skin prick test

Recent studies showed the prevalence of adult AD to be considerably higher than previously thought[6-8] and remain fairly constant across all adult ages.[8]

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Many adults with AD might have child-onset AD, with disease persisting into adulthood. However, a recent systematic review and meta-analysis found that across all studies only 20% of children did not have a period of observed disease clearance by 8 years of follow-up.[9] Although persistence of child-onset AD is common, it might not fully explain the observed high prevalences of adult AD.

Another factor contributing to the high prevalence of adult AD is adult-onset AD. Previous studies reported varying rates of adult-onset AD. We hypothesized that adult-onset AD is commonly reported and encompasses a distinct clinical phenotype. We conducted a systematic review and meta-analysis to explore how commonly adult-onset AD occurs and its clinical characteristics.

CAPSULE SUMMARY

- Previous studies have yielded conflicting data regarding how often atopic dermatitis persists or remits.
- Approximately 1 in 4 adults with atopic dermatitis report adult-onset disease, with similar proportions across different countries.
- Adult-onset atopic dermatitis is associated with different morphologic and historical characteristics than child-onset atopic dermatitis.

METHODS

Literature search

The following databases were searched for articles up to December 1, 2017: Cochrane Library, Medline (PubMed and Ovid), Embase, GREAT (Global Resource of EczemA Trials), LILACS (Latin American and Caribbean Health Sciences Literature) and Scopus. The search strategy was modified from a previous Cochrane review of AD[10] to also include a number of search terms related to age of disease onset (Supplemental Table I; available at http://www.jaad.org).[11-13]

Any cross-sectional or cohort study was included that contained analyses on the age of AD onset after 10 years of age; had a sample size of at least 100 AD patients; and was published online, in print, or in press from the earliest entry in the respective database up to December 1, 2017. We included articles written in any language. Title and abstract review was performed independently by at least 2 reviewers (Mr Lee, Mr Patel, Mr Singam, and Mr Rastogi), and conflicts were resolved by discussion. Studies were excluded on the basis of the title or abstract if there was no clear indication of analysis of age of onset, if the study size included <100 AD patients, or had a case-control study design. Full-text review was performed by at least 2 reviewers. Foreign language manuscripts were translated. If data were duplicated in >1 study, the most recent and complete study was included. Studies were excluded after full-text review if age of AD onset data was not presented. This study was exempt from institutional review board approval at Northwestern University Feinberg School of Medicine because data were gathered from published literature.

Data extraction

Data extraction was performed by at least 2 reviewers. The following data were extracted: first author; year of publication; source of funding; study design; method of AD diagnosis; AD diagnostic criteria utilized; study blinding; geographic region of the study; distribution of race/ethnicity, age of AD onset, AD duration, age, and sex; inclusion of patch testing, skin biopsy, or skin prick; personal history of childhood AD and other allergic diseases, habitation; follow-up confirmation of adult-onset AD diagnosis; family history of allergic diseases; lesion morphology and distribution; and phenotype of AD.

Data analysis

Statistical analysis was performed using MedCalc for Windows, version 18.0 (MedCalc Software, Ostend, Belgium). Data visualization was performed using MATLAB Release 2016b (The MathWorks Inc, Natick, MA).

RESULTS

Literature search

Overall, 4074 nonduplicate citations were identified in the database search; 3690 were excluded during title and abstract review and 359 during full-text review. In total, 25 observational studies met inclusion and exclusion criteria and were included in this systematic review (Fig 1).[14]

Study characteristics

The 25 observational studies were published during 1956-2017.[5,11-13,15-35] Six (24%) studies had prospective cohorts, 4 (16%) had retrospective cohorts, and 15 (60%) had cross-sectional cohorts. Funding was reported in 15 (60%) studies, with 3 (20%) funded federally, 5 (33.3%) funded by a foundation, 2 (13.3%) funded federally and by a foundation, 2 (13.3%) funded by a pharmaceutical company, 2 (13.3%) unfunded, and 1 (6.7%) funded by a hospital.

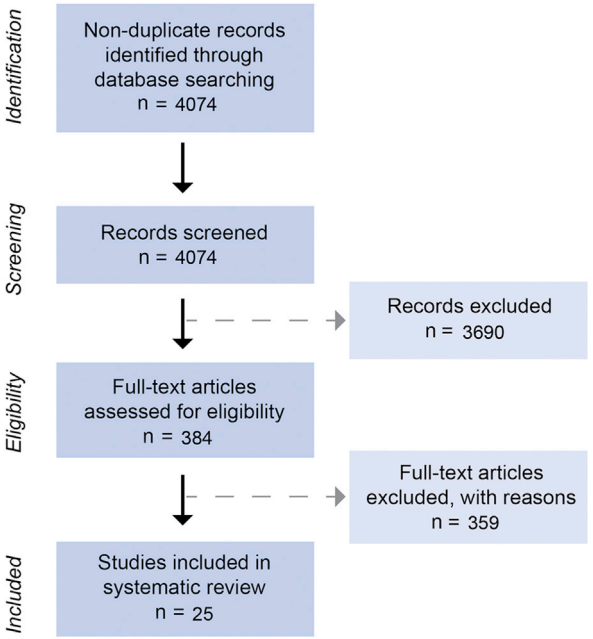

Fig 1. PRISMA (preferred reporting items for systemic reviews and meta-analyses) flow diagram.[14]

The studies were conducted across 16 countries, including 11 (44%) in Europe, 10 (40%) in Asia, 2 (8%) in America, and 2 (8%) in other regions. Eleven (44%) studies were performed in adults, 1 (4%) in children and adolescents, and 13 (52%) in both. Race/ethnicity was reported in 8 (32%) studies, with only 2 (8%) reporting inclusion of any black patients.

AD was diagnosed clinically in 17 studies (68%), most commonly with the Hanifin and Rajka criteria in 11 (44%), followed by the UK Working Party criteria in 2 (8%), Japanese Dermatological Association criteria in 2 (8%), Eczema Prevalence Impact Working Group diagnostic criteria in 1 (4%), other clinical criteria in 3 (12%), and unspecified in 6 (24%). AD diagnosis was made with other approaches in 8 (32%) studies, including self-reporting in surveys in 4 (16%), reviewing of health records in 2 (8%), reviewing of codes from claims data in 1 (4%), and unspecified in 1 (4%).

Proportion of adult-onset AD

Seventeen studies reported age of AD onset as after 16 years of age and had sufficient data for meta-analysis.* Because of significant heterogeneity (I^2 = 99.3%), the pooled meta-analysis of the proportion of adult-onset AD was determined by using random-effects weighting. The pooled proportion of adult-onset AD was 26.1% (95% confidence interval [CI] 16.5%-37.2%) (Fig 2).

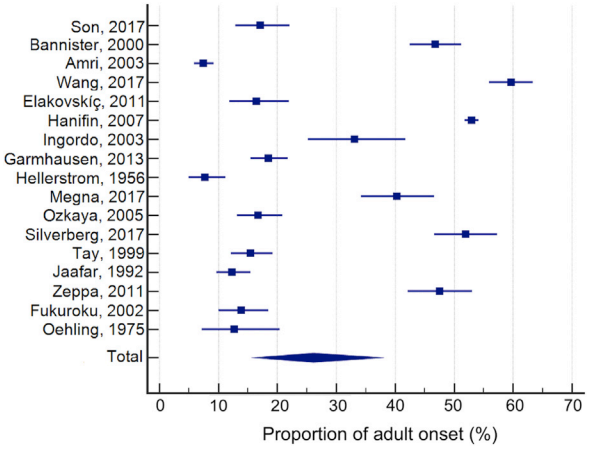

Fig 2. Forest plot of the proportion of adult-onset atopic dermatitis (AD). The proportion of adult-onset AD, 95% confidence intervals (*squares*), and pooled proportion of adult-onset AD (*diamond*) are presented.

Similar results were found in studies that used clinical diagnosis (25.1%, 95% CI 15.2%-36.4%) as opposed to another approach (29.7%, 95% CI 11.1%-52.9%). The highest proportion of adult-onset AD was observed in the United States (53.0%, 95% CI 51.8%-54.1%), with lower and consistent proportions in Europe (24.0%, 95% CI 13.6%-36.3%), Asia (21.4%, 95% CI 8.2%-38.7%), and other regions (24.3%, 95% CI 0.2%-69.2%).

Most studies, particularly those that assessed older cohorts, showed that AD onset was well distributed across older ages (Fig 3). Seven studies presented the proportion of AD onset by age 5 years and found widely varying estimates (21.9%, 24.7%, 28%, 58%, 62%, 66.2%, and 86%).

Five of 17 studies reported the proportion of adult-onset and child-onset AD by sex.[22,24,29,30,35] A similar proportion of women (29.2%, 95% CI 15.0%-45.9%) and men (29.9%, 95% CI 14.0%-48.8%) were observed to have adult-onset disease.

Confirmation of adult-onset AD

Five studies retrospectively examined medical records to confirm that patients with adult-onset AD did not have AD in childhood.[12,17,21,27,31] In addition, 3 studies prospectively followed patients from birth to 16 years, birth to 18 years, and from 8th grade to 15 years later to verify that the diagnosis of AD was correct and did not change over time.[23,25,28]

Skin prick test (SPT), patch test, and skin biopsy

Eight of 25 studies documented use of SPTs.† Of those studies, only 1 specified the allergens

*[11,12,16,17,19,20,24,26,27,29-31,33,35]

†[11,17,19,23,25,27,29,35]

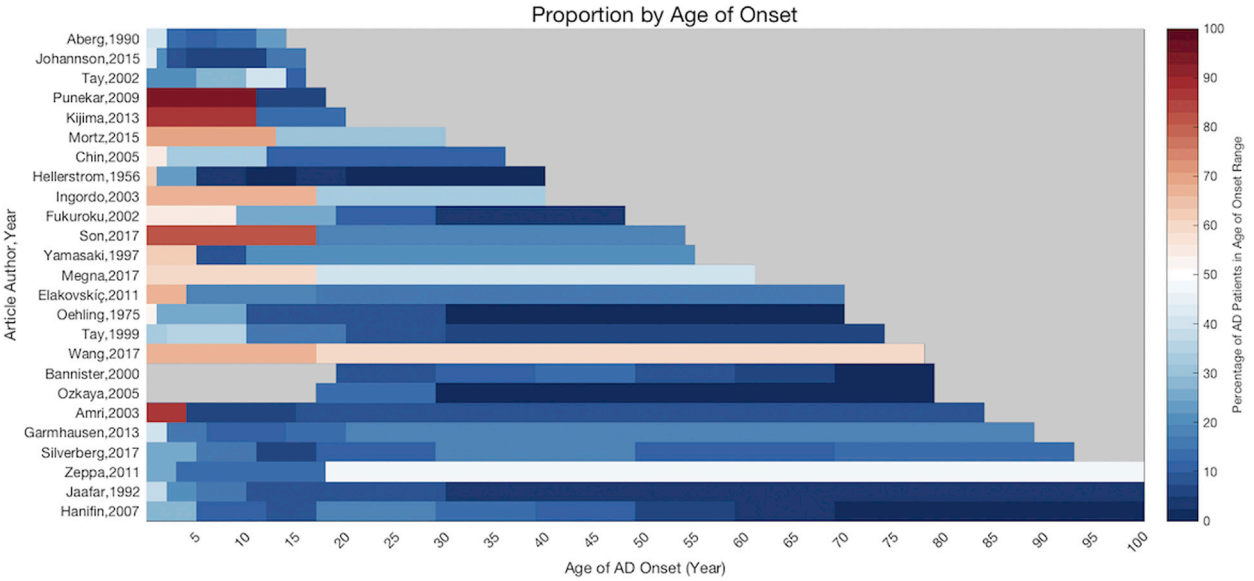

Fig 3. Heat map of the distribution of age of AD onset. The proportion of patients within published age bins are plotted using a color-coded heat map (0% = dark blue; 100% = dark red). *AD*, Atopic dermatitis.

tested. In 1 study of 332 AD patients, SPTs were positive for reactions to *Gramineae* mix (34.6%), *Dermatophagoides pteronyssinus* (28.3%), *Dermatophagoides farinae* (25.30%), *Olea europaea* (15.7%), *Cupressus sempervirens* (14.5%), *Plantaginaceae* mix (12.3%), *Parietaria* mix (10.8%), *Corylus avellana* (9.3%), *Compositae* mix (8.13%), *Betulaceae* mix (6.9%), animal dandruff (5.4%), *ambrosiae* mix (4.2%), tomato (1.5%), fish mix (1.2%), apple (1.2%), hazelnut (1.2%), kiwi (1.2%), cow's milk (0.9%), and chicken egg white (0.9%). No studies presented results of SPTs stratified by the age of AD onset.

Eight studies reported patch test results.[‡] However, only 1 specified the panels used, which included the standard series (GIRDCA [Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali] or SIDAPA [Società Italiana di Dermatologia Allergologica Professionale e Ambientale] with integrative haptens) and atopy patch test. Among those studies, AD patients reacted to at least 1 of 17 different substances. Some notable contact allergens included nickel sulfate, potassium dichromate, cobalt chloride, colophony, and fragrance mix. The substance most commonly tested and with the highest rate of positive reactions was nickel sulfate (n = 4; 0.41%-49.4%). No studies presented patch testing results stratified by age of AD onset.

Only 1 study documented the use of skin biopsy to rule out other disorders.[29] In this article, 65 of 66 biopsies from adult-onset AD patients showed spongiotic dermatitis with eosinophils, with no findings suggestive of cutaneous T-cell lymphoma.

Relationship between area of habitation and age of AD onset

Three studies stratified area of habitation by age of AD onset.[24,30,33] Two studies examined urban versus rural dwellings: 1 study found that a higher proportion (87.5% vs 82.3%) and the other that a lower proportion (70.6% vs 83.4%) of AD patients living in urban areas had adult-onset versus child-onset disease. One study stratified regions of China by ranges of latitude (20°N-45°N in intervals of 5°N) with regions in more northern latitudes being associated with lower average summer temperatures; however, the study did not show a correlation between adult-onset AD prevalence and latitude; the 2 regions with the highest proportion of adult-onset AD was 40°N-45°N (85.2%) and 25°N-30°N (79.7%).

Phenotype and characteristics of AD

Four studies stratified phenotype and morphology by age of AD onset (Fig 4).[11,29,30,33] In individual studies and the pooled analysis, higher proportions of some phenotypes and morphologies were consistently seen more often for child-onset AD than adult-onset AD: facial dermatitis, conjunctivitis or eyelid dermatitis, cheilitis, pruritus after

‡11,17,22,25,27,29,31,35

Characteristic	Number of Studies	Frequency of studies with higher proportions	Age of onset	Random Effects Proportion % (95% CI)	Pooled sample size
Face	3	3	Child-onset	45.0% (30.0-60.5%)	571
		0	Adult-onset	20.6% (13.1-29.3%)	600
Conjunctivitis/Eyelids	2	2	Child-onset	37.0% (10.3-69.1%)	482
		0	Adult-onset	14.6% (2.3-34.8%)	556
Cheilitis	2	2	Child-onset	33.0% (23.5-43.2%)	439
		0	Adult-onset	14.2% (8.0-21.9%)	197
Trunk	2	1	Child-onset	25.8% (20.0-32.1%)	321
		1	Adult-onset	26.5% (3.2-61.4%)	92
Nipples	2	1	Child-onset	15.2% (12.0-18.7%)	439
		0	Adult-onset	9.0% (1.7-21.0%)	197
Feet	2	0	Child-onset	5.6% (2.4-10.0%)	364
		0	Adult-onset	9.0% (6.6-11.9%)	451
Flexural Dermatitis	3	2	Child-onset	62.2% (50.6-73.1%)	714
		0	Adult-onset	53.4% (37.5-68.9%)	604
Nummular	2	1	Child-onset	20.3% (.1-61.0%)	439
		1	Adult-onset	22.7% (7.1-43.7%)	197
Xeroderma/Xerosis	3	2	Child-onset	67.7% (56.8-77.7%)	714
		0	Adult-onset	62.8% (47.3-77.0%)	604
Pruritis After Sweating	2	2	Child-onset	59.0% (43.8-73.4%)	439
		0	Adult-onset	49.8% (28.2-71.3%)	197
Dennie-Morgan Line	2	1	Child-onset	18.1% (.1-55.9%)	439
		0	Adult-onset	8.6% (3.7-15.4%)	197
Hands and Feet	2	1	Child-onset	27.4% (4.0-93%)	439
		0	Adult-onset	18.5% (.6-67.9%)	197
White Dermatographism	2	0	Child-onset	3.4% (1.9-5.3%)	439
		0	Adult-onset	4.5% (2.1-7.8%)	197
Personal History of Allergic Disease	3	0	Child-onset	59.6% (44.0-74.2%)	629
		2	Adult-onset	71.1% (54.2-85.4%)	685
Personal History of Asthma	4	1	Child-onset	20.9% (5.6-42.5%)	865
		1	Adult-onset	18.8% (13.6-24.7%)	706
Personal History of Allergic Rhinitis	4	1	Child-onset	42.9% (27.0-59.6%)	865
		0	Adult-onset	36.4% (23.5-50.3%)	706
Personal History of Conjunctivitis	2	0	Child-onset	19.1% (11.2-28.5%)	426
		1	Adult-onset	24.2% (18.3-30.6%)	509
Family History of Allergic Disease	2	1	Child-onset	51.7 (47.0-56.4%)	429
		1	Adult-onset	60.1% (26.2-89.3%)	221
Family History of Atopic Dermatitis	2	1	Child-onset	37.7 (6.6-76.3%)	358
		0	Adult-onset	26.2 (13.2-41.7%)	251

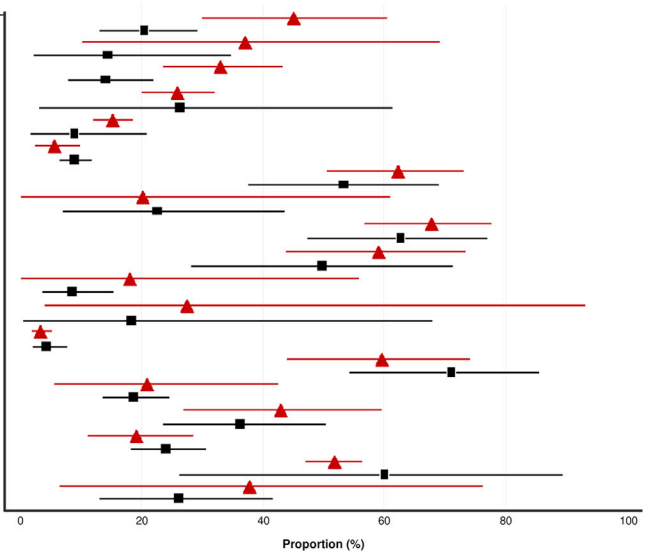

Fig 4. Difference in characteristics between adult-onset and child-onset atopic dermatitis. The pooled proportion of specific characteristics are stratified by age of onset: adult (*black*) versus child (*red*). *CI*, Confidence interval.

sweating, xeroderma or xerosis, hand and foot dermatitis, nipple dermatitis, and Dennie-Morgan line (Supplemental Table II; available at http://www.jaad.org).[11,29,30,33] In individual studies and the pooled analysis, child-onset AD was consistently associated with a lower proportion of lesions on the feet and white dermatographism. Inconsistent patterns were observed for the trunk, nummular eczema, and flexural dermatitis among individual studies.

Five studies stratified personal and family history of atopic disease by age of AD onset (Supplemental Table III; available at http://www.jaad.org).[11,24,29,30,33] There were no consistent patterns of atopic disease across all studies. However, in some individual studies and the pooled analysis, there was a lower proportion of child-onset AD patients than adult-onset AD patients with a personal history of any allergic disease, particularly conjunctivitis, and a family history of allergic disease. In contrast, a higher proportion of patients with child-onset AD than adult-onset AD had a personal history of allergic rhinitis. There were no differences in asthma history between those with child-onset and adult-onset AD.

One study stratified personal and family history of adverse reactions and allergies to food and medications by age of AD onset.[29] A higher proportion of patients with child-onset AD than adult-onset AD had a personal or family history of food or medication allergies and adverse reactions.

DISCUSSION

The results of this systematic review and meta-analysis of observational studies suggest that ~1 in 4 adults with AD report adult-onset disease, with relatively consistent proportions of adult-onset disease for both sexes across different regions. There were several important characteristics that seemed to differ between adult-onset and child-onset AD, including higher proportions of foot dermatitis and lower proportions of flexural eczema and multiple other signs and symptoms.

Some have questioned whether adult-onset AD is fact or fancy? It is possible that patients with self-reported adult-onset disease had active AD early in life that remitted and was forgotten. Such cases would be adult-recurrent rather than adult-onset AD. The important clinical take-home message is that patients who report adult-onset of their AD symptoms (whether they are correct or not) can have AD and respond to appropriate AD therapy. In addition, 5 studies included in this systematic review retrospectively examined patient medical records and found no evidence of AD earlier in life. From those studies and the distinct characteristics observed for adult-onset AD across studies, it appears that adult-onset AD is a real phenomenon and distinct subset from persistent child-onset AD. Future studies are needed to determine the pathomechanisms, triggers, and clinical course of adult-onset AD.

Some studies have suggested that 50% of AD cases begin in the first year of life and that 85% begin by age 5 years.[2-4] However, it is important to recognize that these studies examined pediatric cohorts 3-11 years of age and were, therefore, unable to determine the age of onset in older populations. The 25 studies included in this systematic review specifically assessed cohorts of adolescents and adults that examined ages of onset ≥10 years. Most studies, particularly those that assessed adults, found considerably lower proportions of disease beginning early in life and conversely higher proportions of adult-onset disease. Moreover, 7 studies reported on and found widely varying estimates for the proportion of AD patients with age of onset by 5 years; 3 of 7 studies found that less than a third of patients had AD onset by age 5 years. Taken together, it appears that AD is not only a disease of childhood; in many patients, the disease begins in adulthood.

This systematic review highlights an important clinical challenge in the assessment of adult AD, ie, proper diagnosis of adult-onset disease. Among the limited number of studies that stratified disease characteristics by age of AD onset, it appears that adult-onset AD is associated with higher rates of foot dermatitis, possibly lower rates of flexural lesions, and lower rates of multiple other signs and symptoms of AD. These clinical characteristics might make adult-onset AD difficult to distinguish from other entities that commonly begin in adulthood, eg, allergic contact dermatitis, cutaneous T-cell lymphoma. It is important for clinicians to consider and rule out the differential diagnosis of AD in adults and consider appropriate work up, eg, patch testing and biopsy. Although patch testing and biopsy are not required to make the diagnosis of AD, they can be helpful to rule out other conditions. Indeed, the recent consensus guidelines for patch testing in patients with AD suggested that all patients with adult-onset AD be patch tested to rule out contact dermatitis.[36] Of note, in 8 studies, patch testing was performed and variable rates of positive and relevant reactions were found; however, allergen avoidance did not resolve the AD in these studies. This review also highlights the need for future studies on adult-onset AD that involve adequate assessment and confirmatory diagnostic testing, as well as the need for a thorough presentation of the frequency and proportion of lesion distribution, morphologic characteristics, associated clinical signs and symptoms, and other clinical characteristics of adult-onset versus child-onset AD.

There are multiple strengths to this meta-analysis, including the use of a comprehensive search strategy, use of multiple reviewers for title and abstract review and data abstraction, random-effect models and multiple sensitivity analyses in meta-analysis. However, there are some potential limitations. Some of the included studies were not primarily focused on investigating adult-onset AD. As a result, proportions of different phenotypes, morphologies, personal and family histories of allergic disease were not assessed in most studies. There were considerable differences in study designs and definitions used for adult-onset AD. Nevertheless, substantial and clinically relevant proportions of adult-onset AD were reported across all studies included in this analysis. Phenotypic characteristics of adult-onset AD were only assessed in 4 studies. Thus, the results might be biased by the study region, design, and methods used and by a lack of population-based controls. We recommend that future studies of adult-onset AD prospectively examine the phenotypic differences with child-onset AD.

In conclusion, AD is not only a disease of childhood. Approximately 1 in 4 adults with AD report symptom onset during adulthood. Adult-onset AD was associated with distinct clinical characteristics. Future studies are needed to determine the true prevalence, incidence, and phenotypic characteristics of adult-onset AD and whether there are differences of disease course and therapeutic response between adult-onset and child-onset AD.

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Supplemental Table I. Literature search strategies

Database	Search strategy
Cochrane	#1 MeSH descriptor: [dermatitis, atopic] explode all trees #2 MeSH descriptor: [eczema] explode all trees #3 MeSH descriptor: [neurodermatitis] explode all trees #4 ''atopic dermatitis'' (word variations have been searched) #5 ''dermatitis atopic'' (word variations have been searched) #6 ''childhood eczema'' (word variations have been searched) #7 ''infantile eczema'' (word variations have been searched) #8 ''besnier's prurigo'' (word variations have been searched) #9 ''neurodermatitis'' (word variations have been searched) #10 ''eczema'' (word variations have been searched) #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 #12 MeSH descriptor: [age of onset] explode all trees #13 ''onset'' (word variations have been searched) #14 ''onset disorders'' (word variations have been searched) #15 ''onset'' and ''disorders'' (word variations have been searched) #16 ''older'' and ''onset'' (word variations have been searched) #17 ''age of onset'' (word variations have been searched) #18 ''late'' and ''onset'' (word variations have been searched) #19 ''adult'' and ''onset'' (word variations have been searched) #20 ''adolescent'' and ''onset'' (word variations have been searched) #21 ''older adults'' (word variations have been searched) #22 MeSH descriptor: [geriatrics] explode all trees #23 ''geriatrics'' (word variations have been searched) #24 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 #25 #11 and #24
Embase[11]	('atopic dermatitis'/exp OR 'atopic dermatitis' OR 'dermatitis atopic' OR 'eczema'/exp OR 'eczema' OR 'childhood eczema' OR 'infantile eczema' OR 'neurodermatitis' OR 'neurodermatitis'/exp OR 'Besnier/s prurigo' OR ('Besnier/s' AND 'prurigo')) AND ('onset age'/exp OR 'onset' OR 'onset disorders' OR ('onset' AND 'disorders') OR 'age of onset' OR ('late' AND 'onset') OR ('older' AND 'onset') OR ('adult' AND 'onset') OR ('adolescent' AND 'onset') OR 'older adults' OR 'geriatrics'/exp OR 'geriatrics')
GREAT	'atopic dermatitis' or 'dermatitis atopic' or 'eczema' or 'childhood eczema' or 'infantile eczema' or 'neurodermatitis' or 'besniers prurigo' AND 'age of onset' or 'onset' or 'onset disorders' or ('late' and 'onset') or ('onset' and 'disorders') or ('older' and 'onset') or ('adult' and 'onset') or ('adolescent' and 'onset') or 'older adults' or 'geriatrics' AND any treatment
LILACS	(tw:(((tw:(atopic dermatitis)) OR (tw:(dermatitis atopic)) OR (tw:(atopic dermatitis)) OR (tw:(eczema)) OR (tw:(childhood eczema)) OR (tw:(infantile eczema)) OR (tw:(neurodermatitis)) OR (tw:(besniers prurigo))))) AND (tw:(((tw:(onset)) OR ((tw:(onset)) AND (tw:(disorders))) OR (tw:(age of onset)) OR ((tw:(onset)) AND (tw:(late))) OR ((tw:(onset)) AND (tw:(older))) OR ((tw:(onset)) AND (tw:(adult))) OR ((tw:(onset)) AND (tw:(adolescent))) OR (tw:(older adults)) OR (tw:(geriatrics))))) AND (instance:''regional'') AND (limit:(''humans''))

Continued

Supplemental Table I. Cont'd

Database	Search strategy
Medline (Ovid)[12]	1 Dermatitis, atopic.mp. or exp DERMATITIS, ATOPIC/ 2 atopic dermatitis.mp. 3 dermatitis atopic.mp 4 exp ECZEMA/ or eczema.mp. 5 childhood eczema.mp. 6 infantile eczema.mp. 7 neurodermatitis.mp. or exp Neurodermatitis/ 8 Besnier's prurigo.mp. 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10 age of onset.mp. or exp ''Age of Onset''/ 11 onset.mp. 12 onset disorders.mp. 13 (''onset'' and ''disorders'').mp. 14 (''late'' and ''onset'').mp. 15 (''older'' and ''onset'').mp. 16 (''adult'' and ''onset'').mp. 17 (''adolescent'' and ''onset'').mp. 18 (''childhood'' and ''onset'').mp. 19 ''older adults''.mp. 20 ''geriatrics''.mp.'' or exp Geriatrics/ 21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 22 9 and 21
Medline (PubMed)	(''Dermatitis, Atopic''[Mesh] OR ''atopic dermatitis''[all fields] OR ''dermatitis atopic''[all fields] OR ''Eczema''[Mesh] OR ''eczema''[all fields] OR ''childhood eczema''[all fields] OR ''infantile eczema''[all fields] OR ''neurodermatitis''[all fields] OR ''Neurodermatitis''[Mesh] OR ''Besnier's prurigo''[all fields] OR (''Besnier's''[all fields] AND ''prurigo''[all fields])) AND (''Age of Onset''[Mesh] OR ''onset''[all fields] OR ''onset disorders''[all fields] OR (''onset''[all fields] AND ''disorders''[all fields]) OR ''age of onset''[all fields] OR (''late''[all fields] AND ''onset''[all fields]) OR (''older''[all fields] AND ''onset''[all fields]) OR (''adult''[all fields] AND ''onset''[all fields]) OR (''adolescent''[all fields] AND ''onset''[all fields]) OR ''older adults''[all fields] OR ''geriatrics''[all fields] OR ''Geriatrics''[Mesh])
Scopus[13]	(TITLE-ABS-KEY (''atopic dermatitis'' OR ''dermatitis atopic'' OR ''eczema'' OR ''childhood eczema'' OR ''infantile eczema'' OR ''neurodermatitis'' OR ''besniers prurigo'') AND TITLE-ABS-KEY (''onset'' OR (''onset'' AND ''disorders'') OR ''onset age'' OR (''late'' AND ''onset'') OR (''older'' AND ''onset'') OR (''adult'' AND ''onset'') OR (''adolescent'' AND ''onset'') OR ''older adults'' OR ''geriatrics''))

LILACS, Latin American and Caribbean Health Sciences Literature; *GREAT*, Global Resource of EczemA Trials; *MeSH*, medical subject heading.

Supplemental Table II. Distribution of lesions, morphologic characteristics, associated clinical signs and symptoms, and other clinical characteristics stratified by age of AD onset

Variable	Study author, year	Age of AD onset, years	Frequency	Proportion, %
Distribution of lesions				
Head and neck	Son et al, 2017[30]	≥18	11/48	22.9
		<18	38/232	16.4
Face	Wang et al, 2017[33]	≥18	68/407	16.7
		<18	141/275	51.3
	Ingordo et al, 2003[11]	≥18	7/44	15.9
		<18	23/89	25.8
	Silverberg et al, 2017[29]	≥18	42/149	28.2
		<18	118/207	57.0
Conjunctivitis and eyelids	Wang et al, 2017[33]	≥18	29/407	7.1
		<18	60/275	21.8
	Silverberg et al, 2017[29]	≥18	36/149	24.2
		<18	111/207	53.6
Neck	Ingordo et al, 2003[11]	≥18	3/44	6.8
		<18	13/89	14.6
Lips and chelitis	Son et al, 2017[30]	≥18	9/48	18.8
		<18	65/232	28.0
	Silverberg et al, 2017[29]	≥18	17/149	11.4
		<18	79/207	38.2
Ears	Wang et al, 2017[33]	≥18	39/407	9.6
		<18	52/275	18.9
Anterior neck folds	Silverberg et al, 2017[29]	≥18	52/149	34.9
		<18	122/207	58.9
Scalp	Silverberg et al, 2017[29]	≥18	35/149	23.5
		<18	96/207	46.4
Posterior auricular	Silverberg et al, 2017[29]	≥18	23/149	15.4
		<18	83/207	40.1
Flexor surface of arms and legs	Son et al, 2017[30]	≥18	14/48	29.2
		<18	119/232	51.3
Arms	Ingordo et al, 2003[11]	≥18	14/44	31.8
		<18	38/89	42.7
Wrists	Ingordo et al, 2003[11]	≥18	4/44	9.1
		<18	7/89	7.9
Hands and feet	Son et al, 2017[30]	≥18	1/48	2.1
		<18	6/232	2.6
	Silverberg et al, 2017[29]	≥18	63/149	42.3
		<18	134/207	64.7
Hands	Ingordo et al, 2003[11]	≥18	26/44	59.1
		<18	31/89	34.8
Antecubital fossa	Ingordo et al, 2003[11]	≥18	7/44	15.9
		<18	18/89	20.2
Feet	Wang et al, 2017[33]	≥18	36/407	8.8
		<18	11/275	4.0
	Ingordo et al, 2003[11]	≥18	4/44	9.1
		<18	7/89	7.9
Legs	Ingordo et al, 2003[11]	≥18	6/44	13.6
		<18	22/89	24.7
Popliteal folds	Ingordo et al, 2003[11]	≥18	4/44	9.1
		<18	13/89	14.6
Trunk	Son et al, 2017[30]	≥18	21/48	43.8
		<18	65/232	28.0
	Ingordo et al, 2003[11]	≥18	5/44	11.4
		<18	19/89	21.3

Continued

Supplemental Table II. Cont'd

Variable	Study author, year	Age of AD onset, years	Frequency	Proportion, %
Nipples	Son et al, 2017[30]	≥18	7/48	14.6
		<18	37/232	15.9
	Silverberg et al, 2017[29]	≥18	7/149	4.7
		<18	29/207	14.0
Flexural dermatitis	Son et al, 2017[30]	≥18	14/48	29.2
		<18	119/232	51.3
	Wang et al, 2017[33]	≥18	264/407	64.9
		<18	173/275	62.9
	Silverberg et al, 2017[29]	≥18	92/149	61.7
		<18	149/207	72.0
Genital	Son et al, 2017[30]	≥18	0/48	0
		<18	2/232	0.9
Extensor surfaces	Son et al, 2017[30]	≥18	1/48	2.1
		<18	2/232	0.9
Hand and foot dermatitis	Son et al, 2017[30]	≥18	6/48	12.5
		<18	63/232	27.2
≥3 Body parts involved	Wang et al, 2017[33]	≥18	217/407	53.3
		<18	203/275	73.8
Morphological characteristics				
Follicular eczema	Silverberg et al, 2017[29]	≥18	7/149	4.7
		<18	11/207	5.3
Nummular eczema	Son et al, 2017[30]	≥18	16/48	33.3
		<18	93/232	40.1
	Silverberg et al, 2017[29]	≥18	21/149	14.1
		<18	12/207	5.8
Associated clinical signs				
Pityriasis alba	Silverberg et al, 2017[29]	≥18	3/149	2.0
		<18	23/207	11.1
Anterior subcapsular cataracts	Silverberg et al, 2017[29]	≥18	8/149	5.4
		<18	6/207	2.9
Keratoconus	Silverberg et al, 2017[29]	≥18	1/149	0.7
		<18	3/207	1.4
Xeroderma/xerosis	Son et al, 2017[30]	≥18	27/48	56.3
		<18	148/232	63.8
	Wang et al, 2017[33]	≥18	224/407	55.0
		<18	167/275	60.7
	Silverberg et al, 2017[29]	≥18	113/149	75.8
		<18	162/207	78.3
Icthyosis	Son et al, 2017[30]	≥18	1/48	2.1
		<18	7/232	3.0
Keratosis pilaris	Son et al, 2017[30]	≥18	2/48	4.2
		<18	26/232	11.2
Palmar hypersensitivity, ichthyosis, keratosis pilaris	Silverberg et al, 2017[29]	≥18	45/149	30.2
		<18	121/207	58.5
Perifollicular accentuation	Son et al, 2017[30]	≥18	4/48	8.3
		<18	32/232	13.8
Orbital darkening	Son et al, 2017[30]	≥18	15/48	31.3
		<18	86/232	37.1
Allergic shiner	Son et al, 2017[30]	≥18	11/48	22.9
		<18	80/232	34.5
Extra infra-orbital crease (ie, Dennie-Morgan line)	Son et al, 2017[30]	≥18	2/48	4.2
		<18	12/232	5.2
	Silverberg et al, 2017[29]	≥18	16/149	10.7
		<18	75/207	36.2

Continued

Supplemental Table II. Cont'd

Variable	Study author, year	Age of AD onset, years	Frequency	Proportion, %
Thinning of outer third of eyebrows (ie, Hertoghe)	Son et al, 2017[30]	≥18	4/48	8.3
		<18	9/232	3.9
White dermatographism	Son et al, 2017[30]	≥18	2/48	4.2
		<18	6/232	2.6
	Silverberg et al, 2017[29]	≥18	6/149	4.0
		<18	8/207	3.9
Erythema	Wang et al, 2017[33]	≥18	194/407	47.7
		<18	223/275	81.1
Vesicles	Wang et al, 2017[33]	≥18	80/407	19.7
		<18	27/275	9.8
Nodules	Wang et al, 2017[33]	≥18	56/407	13.8
		<18	11/275	4.0
Associated symptoms				
Pruritus after sweating	Son et al, 2017[30]	≥18	18/48	37.5
		<18	119/232	51.3
	Silverberg et al, 2017[29]	≥18	90/149	60.4
		<18	138/207	66.7
Intolerance to wool	Son et al, 2017[30]	≥18	14/48	29.2
		<18	80/232	34.5
Palmar hypersensitivity	Son et al, 2017[30]	≥18	3/48	6.3
		<18	38/232	16.4
Food intolerance	Son et al, 2017[30]	≥18	7/48	14.6
		<18	32/232	13.8
Metal intolerance	Son et al, 2017[30]	≥18	8/48	16.7
		<18	29/232	12.5
Course worsened by environmental or emotional factors	Silverberg et al, 2017[29]	≥18	116/149	77.9
		<18	182/207	87.9
Other clinical characteristics				
Photosensitivity	Son et al, 2017[30]	≥18	4/48	8.3
		<18	19/232	8.2
Tendency toward cutaneous infections	Silverberg et al, 2017[29]	≥18	28/149	18.8
		<18	64/207	30.9
Bacterial skin infection	Son et al, 2017[30]	≥18	1/48	2.1
		<18	16/232	6.9
Fungal skin infection	Son et al, 2017[30]	≥18	1/48	2.1
		<18	8/232	3.4
Molluscum contagiosum	Son et al, 2017[30]	≥18	0/48	0
		<18	2/232	0.9
Nickel allergy	Son et al, 2017[30]	≥18	6/48	12.5
		<18	33/232	14.2

AD, Atopic dermatitis.

Supplemental Table III. Proportion of personal and family history of allergic disease stratified by age of atopic dermatitis onset

Characteristic	Study author, year	Age of AD onset, years	Frequency	Proportion, %
Personal history of allergic disease	Wang et al, 2017[33]	≥18	333/407	81.8
		<18	202/275	73.5
	Megna et al, 2017[24]	≥18	52/102	51.0
		<18	80/151	53.0
	Silverberg et al, 2017[29]	≥18	136/176	77.3
		<18	104/203	51.2
Personal history of atopic dermatitis alone	Ingordo et al, 2003[11]	≥18	28/44	63.6
		<18	46/89	51.7
Personal history of asthma	Son et al, 2017[30]	≥18	4/48	8.3
		<18	23/232	9.9
	Wang et al, 2017[33]	≥18	78/407	19.2
		<18	19/275	6.9
	Megna et al, 2017[24]	≥18	28/102	27.5
		<18	37/151	24.5
	Silverberg et al, 2017[29]	≥18	26/149	17.4
		<18	104/207	50.2
Personal history of allergic rhinitis	Son et al, 2017[30]	≥18	22/48	45.8
		<18	109/232	47.0
	Wang et al, 2017[33]	≥18	87/407	21.4
		<18	60/275	21.8
	Megna et al, 2017[24]	≥18	46/102	45.1
		<18	72/151	47.7
	Silverberg et al, 2017[29]	≥18	55/149	36.9
		<18	118/207	57.0
Personal history of conjunctivitis	Wang et al, 2017[33]	≥18	89/407	21.9
		<18	41/275	14.9
	Megna et al, 2017[24]	≥18	29/102	28.4
		<18	36/151	23.8
Personal history of food allergy and adverse reaction	Silverberg et al, 2017[29]	≥18	22/149	14.8
		<18	87/207	42.0
Personal history of medication adverse reaction	Silverberg et al, 2017[29]	≥18	43/149	28.9
		<18	64/207	30.9
Family history of allergic disease	Son et al, 2017[30]	≥18	20/48	41.7
		<18	116/232	50.0
	Silverberg et al, 2017[29]	≥18	132/173	76.3
		<18	106/197	53.8
Family history of atopic dermatitis	Megna et al, 2017[24]	≥18	19/102	18.6
		<18	29/151	19.2
	Silverberg et al, 2017[29]	≥18	50/149	33.6
		<18	120/207	58.0
Parental history of atopic dermatitis	Son et al, 2017[30]	≥18	4/48	8.3
		<18	8/232	3.4
Sibling history of atopic dermatitis	Son et al, 2017[30]	≥18	6/48	12.5
		<18	32/232	13.8
Family history of asthma	Silverberg et al, 2017[29]	≥18	28/149	18.8
		<18	86/207	41.5
Parental history of atopic dermatitis	Son et al, 2017[30]	≥18	4/48	8.3
		<18	1/232	0.4
Sibling history of atopic dermatitis	Son et al, 2017[30]	≥18	2/48	4.2
		<18	1/232	0.4
Family history of allergic rhinitis	Silverberg et al, 2017[29]	≥18	33/149	22.1
		<18	71/207	34.3
Parental history of allergic rhinitis	Son et al, 2017[30]	≥18	3/48	6.3
		<18	32/232	13.8

Continued

Supplemental Table III. Cont'd

Characteristic	Study author, year	Age of AD onset, years	Frequency	Proportion, %
Sibling history of allergic rhinitis	Son et al, 2017[30]	≥18	6/48	12.5
		<18	21/232	9.1
Family history of food allergy and adverse reaction	Silverberg et al, 2017[29]	≥18	14/149	9.4
		<18	47/207	22.7
Family history of medication adverse reaction	Silverberg et al, 2017[29]	≥18	12/149	8.1
		<18	28/207	13.5