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Patient impact and economic burden of mild to moderate atopic dermatitis

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Transparency

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Abstract

Objective: To present a systematic review of studies conducted to evaluate patient impact and economic burden of mild to moderate atopic dermatitis.

Methods: A MEDLINE (via PubMed), Excerpta Medica database (Embase), and Cochran Library search for English-language articles published January 1, 1996, to December 31, 2016, was performed. Abstracts were manually reviewed from 2015 to 2016 from 10 leading conferences and congresses associated with atopic dermatitis. Manuscripts were reviewed for inclusion in 2 main categories within the review: patient impact of mild to moderate atopic dermatitis and economic burden of atopic dermatitis. Excluded from this data set were any patients in these studies who had severe atopic dermatitis, moderate to severe atopic dermatitis, or atopic dermatitis of unspecified severity.

Results: In total, 222 studies qualified for inclusion in the analysis; this report focuses on the 76 studies that reported results stratified by disease severity. Measured by general and specific instruments, even mild to moderate atopic dermatitis reduces the overall quality of life of patients and their caregivers/families. Disease severity assessed by validated severity instruments directly correlated with quality of life. Treatment of atopic dermatitis can improve the quality of life of patients and their caregivers/families by alleviation of symptoms and reduction in severity. In general, total costs increased as disease severity increased; even mild atopic dermatitis imposed substantial costs.

Conclusions: Our results emphasize the impact of atopic dermatitis, especially mild atopic dermatitis, on patient lives and finances, including education of clinicians, payers, and patients regarding benefits associated with treatment adherence.

Keywords: atopic dermatitis, quality of life, health care economics, health impact assessment

Short title: Patient Impact and Economic Burden of Mild to Moderate AD

Introduction

Atopic dermatitis (AD) is a complex inflammatory disorder that presents as a pruritic inflammatory skin disease that follows a relapsing course^{1,2}. Diagnosis is made clinically and typically consists of at least 3 of the following observations: pruritus, chronic or relapsing dermatitis, personal or family history of atopy, and either flexural lichenification or linearity in adults or facial and extensor involvement in infants and children^{1,3}. AD persists from childhood or can occur in adulthood^{4–6}, suggesting a continuing need for treatment⁷. The goals of treatment of AD are to improve skin barrier function, relieve pruritus, suppress inflammation, and improve patient quality of life (QoL)⁸. The most common treatments at the time of the current systematic review (December 2016) were topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs)⁸.

Most cases of pediatric AD are mild or moderate; for example, in the prospective 2007 National Survey of Children's Health (aged 0–17 years), 67% of cases were mild and 26% were moderate, as reported by the parent/guardian⁹. In the 2013 National Health and Wellness Survey of adults aged ≥18 years, 349 participants had been diagnosed with AD by a physician; of these, 146 (47.7%) self-reported mild AD and 131 (42.8%) reported moderate disease¹⁰.

Currently, there is no standardized measurement of severity of AD². The most common severity scales used in clinical trials incorporate objective and subjective disease features and include the SCORing Atopic Dermatitis (SCORAD) index, the Eczema Area and Severity Index (EASI), and the Investigator's Global Assessment; however, they are not typically used in clinical practice¹¹. The US Food and Drug Administration recommends that a global assessment be a primary end point for new drug applications in AD; a recent systematic review identified 20 different names for global assessments¹². The number of severity scales for AD contributes to the difficulty comparing efficacy of treatment across clinical trial results².

The impact on patients and the economic burden of AD are often underestimated. For example, there is a discordance in the assessment of AD severity between clinicians and patients, including an underassessment of the impact of AD on patient QoL by physicians¹³. AD affects patients and their families considerably, leading to reduced QoL and more psychological and psychosocial comorbidities¹⁴. AD also imposes an economic impact owing to cost of treatment, time lost from work, and over-the-counter treatments, among other issues¹⁴. Herein, we present a systematic review of studies that evaluated patient impact and economic burden of mild to moderate AD.

Methods

Our strategy consisted of searching MEDLINE (via PubMed; Table S1), the Excerpta Medica database (Embase; Table S2), and the Cochrane Library (Table S3) for English-language articles published from January 1, 1996, to December 31, 2016 (Figure 1). Additional literature sources were used to identify data sources beyond manuscripts in peer-reviewed journals. Abstracts were manually reviewed from 2015 to 2016 from 10 leading conferences and congresses associated with AD: the American Academy of Pediatrics; the American Academy of Allergy, Asthma, and Immunology; the American Academy of Dermatology; the American College of Allergy, Asthma and Immunology; the European Academy of Dermatology and Venereology; the European Academy of Pediatrics; the European Society for Pediatric Dermatology; the International Symposium on Atopic Dermatitis; the Society for Pediatric Dermatology; and the World Congress of Pediatric Dermatology. Identified citations were then hand-selected using the established inclusion/exclusion criteria. In brief, publications included in the review enrolled ≥ 25 patients with mild or moderate AD, at least 1 intervention, reporting of economic outcomes and/or patient-reported outcomes (PROs), and were not phase 1 trials (Table S4). Data for severe patient populations were excluded from discussion.

In total, 222 studies qualified for inclusion in the analysis. This report focuses on the 76 studies that reported results stratified by AD disease severity (Figure 1). Manuscripts for these studies were reviewed for inclusion in 2 main categories within the review: patient impact of mild to moderate AD and economic burden of AD. We excluded data for any patients in these studies who had severe AD, moderate to severe AD, or AD of unspecified severity.

Results

Patient Impact of Mild to Moderate AD

Overall Impact of AD on QoL

The effect of AD on QoL has been assessed by generic (i.e. non–disease-specific or dermatology-specific) and dermatology- and AD-specific instruments¹⁵. The most common instruments used by the studies in the current review were the Children’s Dermatology Life Quality Index (CDLQI; age range 4–16 years); the Dermatology Life Quality Index (DLQI); the Dermatology-Specific Quality of Life; the EuroQoL 5 Dimensions (EQ-5D); the Infant’s Dermatitis Quality of Life Index (IDQoL); the 12-item Short-Form Health Survey (SF-12); the 36-item Short-Form Health Survey (SF-36); and the Skindex-16 (Table S4). To aid in the clinical interpretation of these assessments, severity banding (or stratification) was used to assist with relating CDLQI and DLQI scores to the patients’ own view of how their condition has impacted their QoL (Table 1)^{16,17}.

As measured by general and specific instruments, AD reduces overall QoL and health-related QoL of patients and their caregivers/families (Figure 2)¹⁴. For example, those with AD ($n=428$) scored lower on the SF-36 physical (47.1 vs. 50.1; $p < .0001$) and mental (42.8 vs. 48.3; $p < .0001$) component summaries than those without AD ($n=74,572$)¹⁸. When the DLQI was originally developed, patients who had atopic eczema ($n=13$) had a mean (standard deviation [SD]) score of 12.5 (4.8) compared with controls who did

not have any dermatologic conditions ($n=100$; mean [SD], 0.5 [1.1])¹⁹; similar differences were observed for the CDLQI (mean [SD], 7.7 [5.6] and 0.4 [0.7] for eczema and controls, respectively)²⁰. In addition, QoL consistently worsens as AD severity increases, regardless of patient age and which dermatology-specific scale is used (e.g. IDQoL, CDLQI, DLQI) (Figure 2).

To further clarify the relationship between QoL and disease severity, we reviewed those studies that used validated disease severity assessments, such as SCORAD²¹, the EASI²², and the Nottingham Eczema Severity Score (NESS)²³, and QoL instruments (Table S5). Disease severity directly correlated with QoL. For example, CDLQI/DLQI scores increased with increasing SCORAD (correlation $p < .001$), with a mean CDLQI/DLQI of 5.30 in those with mild SCORAD, 8.59 in those with moderate SCORAD, and 11.94 in those with severe SCORAD²⁴. Similar correlations were observed in other studies and with IDQoL^{25,26}. The CLDQI has also been shown to correlate with NESS ($p = 0.66$; $p < .001$)²⁷, and its components have shown correlations with EASI, ranging from 0.60 to 0.74 ($p < .01$)²⁸.

A significant correlation ($p < .0005$) was also found between patient SCORAD and the Dermatitis Family Impact (DFI) questionnaire, which assesses the impact on parents/caregivers/families of patients: mild AD had mean DFI of 3.38, moderate AD had mean DFI of 8.1, and severe AD had mean DFI of 12.8.²⁹ Correlations between disease severity assessed by EASI or SCORAD and QoL were also observed with general functioning QoL scales (i.e. EQ-5D, SF-36, SF-12, short form-6 dimension [SF-6D])^{18,25,30–33}. For example, patients with moderate AD by SCORAD had a DQLI mean of 6.8 and those with severe AD had a DLQI of 10.2 ($p < .001$).^{24,25,32,34,35} Overall, regardless of whether the QoL instrument was dermatology specific or general, mild AD substantially impaired QoL of patients, and the impact of AD on QoL increased further for patients with moderate AD.

Physical Health and Functioning

Dry, itchy, painful skin and sleeping difficulties are key symptoms that negatively impact the physical health and functioning of patients, even those with mild disease (Figure 3)^{4,32,34–38}. Variables that affected infant QoL included itching and time to falling asleep^{25,26,39}. Variables that affected children also included itching and sleep, study, leisure, dressing, and treatment^{24,25,28,34,40}. Variables that affected adults included itching and a wide variability in activities of functioning, such as getting dressed, work/study, leisure activities, and bathing^{24,25,28,32,34,35}. These effects were observed across the disease severity spectrum.

Emotional Well-Being and Social Functioning

In addition to physical health and functioning, mental health sequelae are a concern (Figure 3). Parents are even able to discern changes in mood in infants with AD^{25,26,39}. As patients age, general mood disturbances also include embarrassment and self-consciousness^{25,34,40}, which continue into adulthood

and can manifest as anxiety or depression^{24,25,32,34,35}. These effects manifest even in mild forms of AD^{34,35,41}. Assessment across patients 4–70 years of age showed that the greatest impact of AD was on vitality, social functioning, and mental health³³.

Impact of Treatments

Treatment of AD can improve QoL of patients and their caregivers/families by alleviation of symptoms and reduction in severity. For example, standard-of-care treatment improves QoL (based on Skindex-16) for those with mild to moderate disease⁴². Treatment with topical calcineurin inhibitors improved QoL, as assessed by the World Health Organization Quality of Life-26 questionnaire (WHOQOL-26)⁴³, EQ-5D, and SF-36³⁰.

Actual and perceived inconveniences and safety limitations of treatments can have an impact on potential benefits to QoL. For example, certain treatments may have a negative impact on QoL because of the treatment method itself, especially in children (e.g. time taken to apply topical treatments and initial pain with application)²⁴. In addition, steroid phobia is a common phenomenon that affects QoL and treatment behaviors among persons with AD, and 38%–81% of patients have this phobia⁴⁴. Persons with steroid phobia are more likely to have negative preconceptions about steroids, such as fear of adverse skin effects, and a resulting history of nonadherence to TCS regimens⁴⁵. Specific fears associated with TCS treatment include application of too much cream; use of cream for too long; use of cream on areas of thin skin; stopping of treatment as soon as possible; and need for reassurance⁴⁴. One study identified that patients with AD and steroid phobia had substantially lower QoL scores (WHOQOL-26) than the general population ($p < .001$) and lower scores than patients with AD who did not have steroid phobia⁴³.

Economic Burden of AD

Direct Costs of AD

Total direct costs of AD were assessed in 9 studies: medications, over-the-counter costs, medical testing and procedure expenses, physician visits, out-of-pocket expenses, transportation, and childcare increased as severity of AD worsened (Table 2). Direct comparison among the studies is difficult because of differences in study design and currency. In general, total direct costs increased as disease severity increased; even mild AD imposed substantial cost^{46–52}. For example, annual direct cost from an 8-year retrospective analysis of children in Germany was US \$164 for mild AD and US \$417 for moderate AD⁴⁹. The largest impact on annual cost for patients with mild AD was rehabilitation clinic expenses (defined as treatment units run by a physician and reimbursed by the health insurance agency to improve the disease course) and physician fees for patients with moderate AD⁴⁹. A cost-effectiveness analysis of TCI ointment compared with conventional treatment showed that the cost of TCI ointment, other medications, and physician visits resulted in daily expenses regardless of treatment regimen⁵⁰.

Indirect Costs of AD

Five studies were conducted to assess indirect costs by disease severity^{46,51,53–55}. Among caregivers of children with AD and adults with AD, productivity loss associated with absenteeism was substantial and increased as disease severity increased, although the loss was consistently lower for those who received

TCl than for those who received standard therapy (defined as continuous skin care with emollients and acute anti-inflammatory treatment for flares)^{18,51,53–55}. For example, a US study showed that almost 50% of the calculated total burden of AD was associated with lost productivity, with parents of older children (4–16 years) experiencing a higher burden than those with younger children (<4 years); the costs also increased as disease severity increased⁵¹. A US survey that assessed the burden of AD in adults showed that absenteeism occurred 3 times more frequently in people with AD than in those without AD¹⁸. Productivity loss was evident even in people with mild AD, with marked impairment in absenteeism (6.5%), presenteeism (20.7%), overall work impairment (23.4%), and activity impairment (28.0%), assessed by the Work Productivity and Activity Impairment questionnaire¹⁸.

Health Care Resource Use

We identified 5 analyses of resource use by disease severity^{4,18,54–56} that demonstrated considerable health care resource use even in patients with mild AD. Children with AD are more likely to use health care resources than those of the same age without AD; the rate of use increases as disease severity increases⁴. No difference was observed in the number of health care provider visits^{18,56} or hospital admissions between patients with mild AD and those with moderate AD, although patients with moderate AD had more emergency room visits¹⁸. Among Canadian patients, the number of health care provider visits increased as disease severity increased: those with mild disease had a mean of 2.31 and 0.19 visits per year, those with moderate disease had a mean of 3.19 and 0.57 visits per year, and those with severe disease had a mean of 5.74 and 0.52 visits per year, to publicly funded and non–publicly funded health care providers, respectively⁵⁴.

Treatment type does not seem to influence resource use, as was shown in a 12-month, pan-European study of patients with moderate AD treated with TCl compared with those treated with vehicle ointment in which mean $\pm$ SD number of inpatient days was 0 and 0.1 ± 0.5 , respectively, and daytime admissions were 0 and $<0.1 \pm 0.2$, respectively⁵⁵.

Conclusions

This systematic review is an important update of the current state of patient impact and economic burden of mild to moderate AD. One limitation of the current review is the lack of a standardized AD disease severity assessment tool, which limits ability to compare data across studies. Despite many studies, patient burden (assessed by QoL) and economic burden of AD continue to be underappreciated by health care providers and payers. The current review shows that even mild to moderate AD, which represents most cases, results in substantial patient impact and economic burden for patients and their families/caregivers. Itching and effect on mood were key contributors to the reduced QoL of patients^{24,25,34,35,40}, and lost productivity and outpatient expenses were key economic burdens^{47,50–52,54,56,57}. Patients with mild AD had better QoL and less economic burden than patients with moderate AD, although it was still considerably worse than those without AD.

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Table 1. Effect of AD on patient's life according to severity bands for dermatology-specific QoL instruments.

Scale	AD severity	Score range	Effect on patient's life	No. of data points	References
CDLQI [*]	Mild	3.8–12.5	Small effect to moderate effect	5	25, 27, 28, 34, 40
DLQI [†]	Mild	5.5–9.5	Small effect to moderate effect	4	25, 28, 34, 40
CDLQI [*]	Moderate	8.6–16.0	Moderate effect to very large effect	5	25, 27, 28, 34, 40
DLQI [†]	Moderate	6.8–13.7	Moderate effect to very large effect	5	25, 28, 32, 34, 40

Abbreviations. AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; QoL, quality of life.

^{*} Effect on patient's life is based on score bands for the CDLQI: 0–1 = no effect, 2–6 = small effect, 7–12 = moderate effect, 13–18 = very large effect, 19–30 = extremely large effect¹⁷.

[†] Effect on patient's life is based on score bands for the DQLI: 0-1 = no effect, 2–5 = small effect, 6–10 = moderate effect, 11–20 = very large effect, 21–30 = extremely large effect¹⁶.

Table 2. Economic burden of mild or moderate AD

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
Total direct costs						
Asia-Pacific	Su (1997) ⁴⁶ , Australia, Aus\$	48	Mild: 38% Moderate: 42% Severe: 21% (R&L)	12 months	Medication, dressings, diet, other eczema management strategies, medical consultations	Mild: Aus\$330 Moderate: Aus\$818
	Kim (2015) ⁴⁷ , South Korea, KRW	34	All severities (EASI)	3 months extrapolated to 1 year	Medications, other dermatologic products, medical tests and procedures, prescription fees, dispensing fees, medication storage fees, consultation fees	Mild: 521,178 (95% CI 343,305.8– 699,049.9) KRW Moderate 619,263 (95% CI 290,420.2– 948,106.4) KRW

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
Europe	Healy (2010) ⁴⁸ , UK, £	NA	Moderate to severe (scale, NR)	12 months	TCI ointment costs	Moderate • Child: £424 TCI ointment vs. £512 standard • Adult: £734 TCI ointment vs. £902 standard
	Thaci (2010) ⁵³ , 10 European countries, €	146	Moderate: 52% Severe: 48% (R&L)	12 months	Patient/family: emollient and skin care products, disease- specific expenses, OOP expenses, transport expenses, child care	Moderate AD in children Patient/family: €98 ± 143 TCI ointment vs. €88 ± 159 standard

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
	Wollenberg (2008) ⁵⁵ , 13 European countries, €	134	Moderate: 58% Severe: 42% (IGA)	12 months	Patient/family: OTC products, nondrug therapies, OOP expenses, travel expenses, copays, child care	Moderate AD in adults Patient/family: €247 ± 214 intervention vs. €318 ± 348 standard
	Weinmann (2003) ⁴⁹ , Germany, USD	91	All severities (SCORAD)	12 months	Medication, doctor fees, hospital inpatient costs, rehabilitation clinic costs, [‡] others (allergy diagnostics, emergency room)	Mild: \$164 Moderate: \$417
	Ricci (2006) ⁵² , Italy, USD	33	Mild: 15% Moderate: 61% Severe: 24% (SCORAD)	Annual	TCS, antihistamines, moisturizers, detergents, home care, special foods, consultation fees	Mild: \$853 Moderate: \$1440

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
North America	Ellis (2006) ⁵⁰ , US, USD	TCI group: 474 Control group: 237	TCI Mild/moderate: 81% (IGA) Control Mild/moderate: 79% (IGA)	12 months	Daily cost: TCI, other medications, physician visits	Mild: TCI: \$8.94 Control: \$2.11 Moderate: TCI: \$16.37 Control: \$4.47
	Fivenson (2002) ⁵¹ , US, USD	107	Mild: 51% Moderate: 29% Severe: 3% Unknown: 17% (R&L)	12 months	Medications, phototherapy, laboratory tests, inpatient, outpatient, and emergency room costs	Mild: \$144 ± 24 (SE) Moderate: \$175 ± 26 (SE)

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
Outpatient costs						
	Kim (2015) ⁴⁷ , South Korea, KRW	34		3 months extrapolated to 1 year	Outpatient therapy, drugs, traditional oriental medical therapy	Mild: 282,850 (95% CI 301,413– 590,151) KRW Moderate: 485,733 (95% CI 129,863– 841,601) KRW
Europe	Ricci (2006) ⁵² , Italy, USD	45	Mild: 20% Moderate: 36% Severe: 45% (SCORAD)	Annual	Consultations, including public hospital or private visits	Mild: \$40 Moderate: \$202
North America	Arnold (2007) ⁵⁶ , US, USD	414	Mild: 82% Moderate: 14% Severe: 5% (IGA)	12 months	Annual cost of unscheduled office visits	Mild: \$91 Moderate: \$95

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
	Ellis (2006) ⁵⁰ , US, USD	TCI group: 474 Control group: 237	TCI Mild/moderate: 81% (IGA) Control Mild/moderate: 79% (IGA)	12 months	Daily cost of physician visits	Mild TCI: \$0.46 Control: \$0.46 Moderate TCI: \$0.69 Control: \$0.69
	Barbeau (2006) ⁵⁴ , Canada, Cdn\$	76	Mild: 42% Moderate: 28% Severe: 30% (self-report)	12 months	Medical visit costs	Mild: Cdn\$50 Moderate: Cdn\$85
	Pharmacy costs					
Europe	Ricci (2006) ⁵² , Italy, USD	45	Mild: 20% Moderate: 36% Severe: 45% (SCORAD)	Annual	Antihistamine costs	Mild: \$47 Moderate: \$40
					TCS or antibacterial drug costs	Mild: \$51 Moderate: \$29

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
North America	Ellis (2006) ⁵⁰ , US, USD	TCI group: 474 Control group: 237	TCI Mild/moderate: 81% (IGA) Control Mild/moderate: 79% (IGA)	12 months	Concomitant medications	Mild TCI: \$1.29 Control: \$1.65 Moderate TCI: \$3.72 Control: \$3.78
	Barbeau (2006) ⁵⁴ , Canada, Cdn\$	76	Mild: 42% Moderate: 28% Severe: 30% (self-report)	12 months	Prescription costs	Mild: Cdn\$72 Moderate: Cdn\$77

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
Other direct costs						
Asia-Pacific	Kim (2015) ⁴⁷ , South Korea, KWR	34	All severities (EASI)	3 months extrapolated to 1 year	Transportation and caregiver costs	Mild: 48,889 (95% CI 24,439– 73,338) KRW Moderate: 41,867 (95% CI 0–107,781) KRW
	Jenner (2004) ⁵⁷ , Australia,	45	Mild: 24% Moderate: 51%	12 months	OOP expenses: TCS	Mild: Aus\$51 Moderate: Aus\$98

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
	Aus\$		Severe: 24% (SASSAD)		OOP expenses: other treatment (books, calamine lotion, laundry/washing detergent, makeup, dust mite spray, sunscreen, contraceptive pill, eye drops, water filter system)	Mild: A\$68 Moderate: A\$120
North America	Barbeau (2006) ⁵⁴ , Canada, Cdn\$	76	Mild: 42% Moderate: 28% Severe: 30% (self-report)	12 months	OTC medications	Mild: Cdn\$19 Moderate: Cdn\$30
					Household expenses	Mild: Cdn\$35 Moderate: Cdn\$109

Region	Author (year), country, currency	Sample size*	AD severity (scale)	Time horizon	Outcome measures [†]	Cost outcome per patient per year (unless otherwise specified)
	Fivenson (2002) ⁵¹ , US, USD	107	Mild: 51% Moderate: 29% Severe: 3% Unknown: 17% (R&L)	12 months	OOP expenses: practitioner visits, copays, medications, medication copays, household items, child care	Mild: \$110 ± 35 (SE) Moderate: \$123 ± 34 (SE)

Abbreviations. AD, atopic dermatitis; Aus\$, Australian dollar; Cdn\$, Canadian dollar; €, euros;

EASI, Eczema Area Severity Index; IGA, Investigator's Global Assessment; KRW, Korean won; NA, not applicable; OOP, out of pocket; OTC, over the counter; £, British pounds sterling; R&L, Raika and Langeland; SASSAD, Six Area Six Sign Atopic Dermatitis Score; SCORAD, Scoring of Atopic Dermatitis; TCS, topical corticosteroid; UK, United Kingdom; US, United States; USD, United States dollars.

* Sample size indicates people with AD.

[†] Outcomes measures were annual costs unless otherwise specified.

[‡] Rehabilitation clinic expenses were defined as treatment units run by a physician and reimbursed by the health insurance agency to improve the disease course.

FIGURE LEGENDS

Figure 1. Literature selection and review process. AD, atopic dermatitis.

Figure 2. Impact of AD on QoL by assessment tool in studies with analysis by disease severity.

(A) IDQoL/CDQLI/DLQI. (B) EQ-5D, SF-12, and SF-36. (C) ADIS, DSQL, Skindex-16. CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; DSQL, Dermatology-specific Quality of Life; EQ-5D, EuroQoL 5 Dimensions; IDQoL, Infant's Dermatitis Quality of Life Index; NR, not reported; SF-12, 12-Item Short-Form Health Survey; SF-36, 36-Item Short-Form Health Survey; UK, United Kingdom; US, United States. * Scores are "normed-based" and converted [mean score of 50 and standard deviation (SD) of 10] to be compared with US "standards," i.e. a representative sample of the US population. Scores above and below 50 are above and below the mean scores of the general US population, respectively.

Figure 3. Key symptoms negatively affecting physical health, well-being, and functioning in infants, children, and adults.

Figure 1.

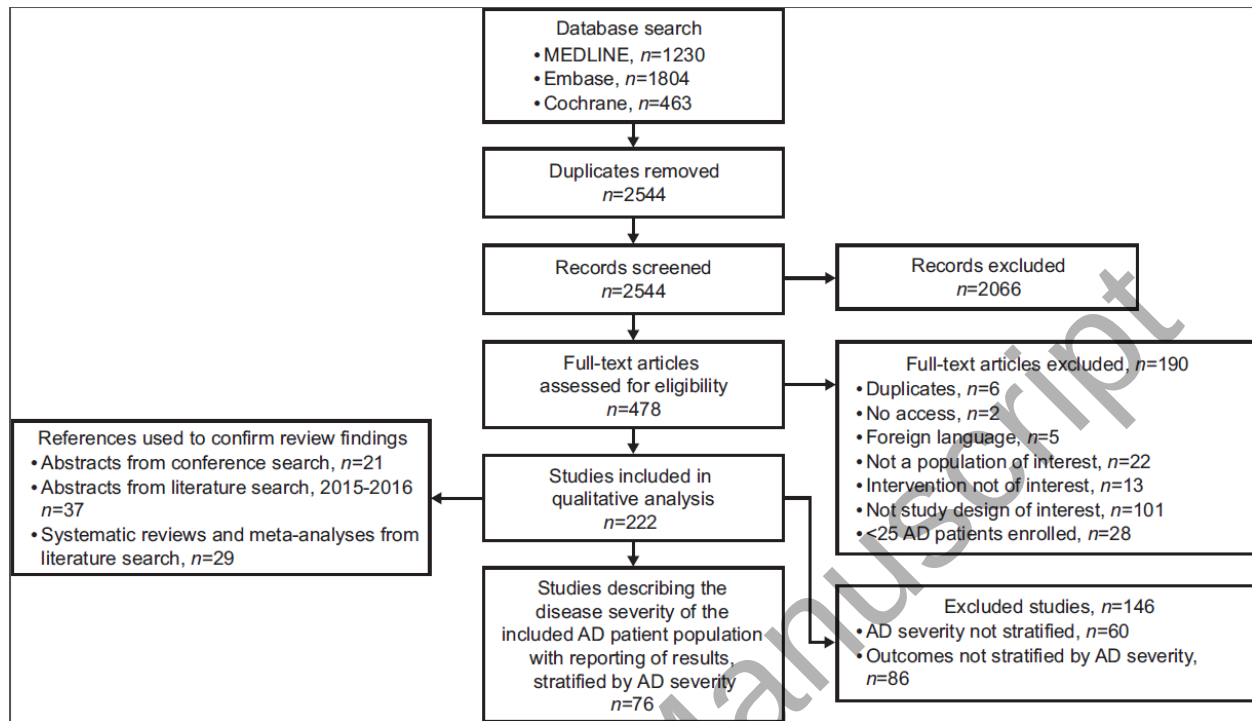
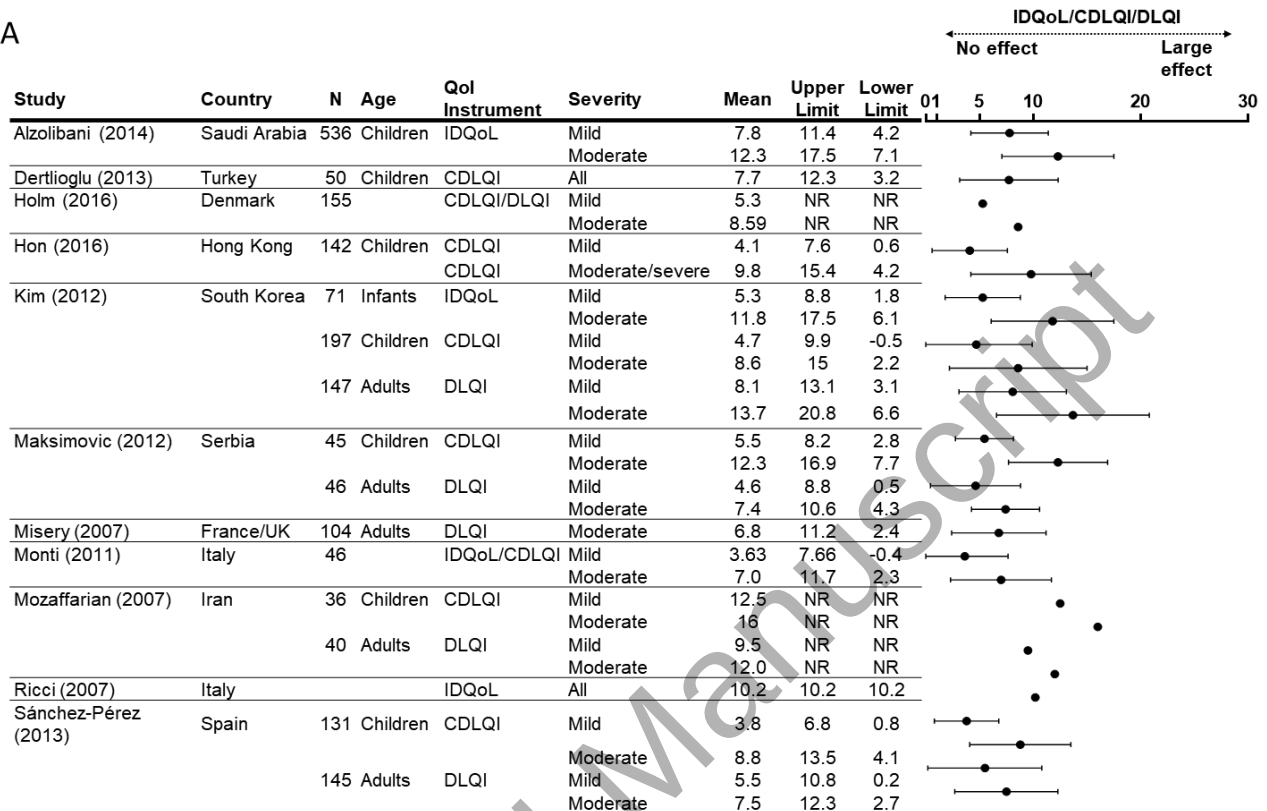
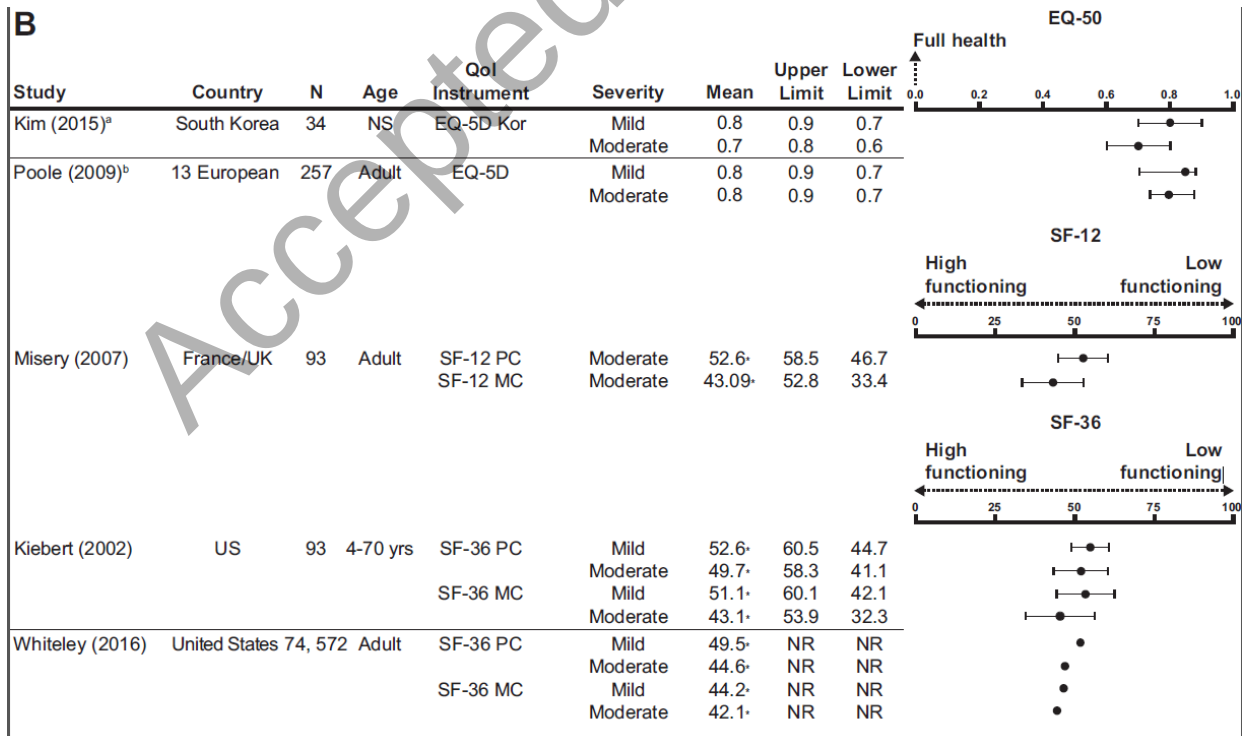


Figure 2.

A



B



C

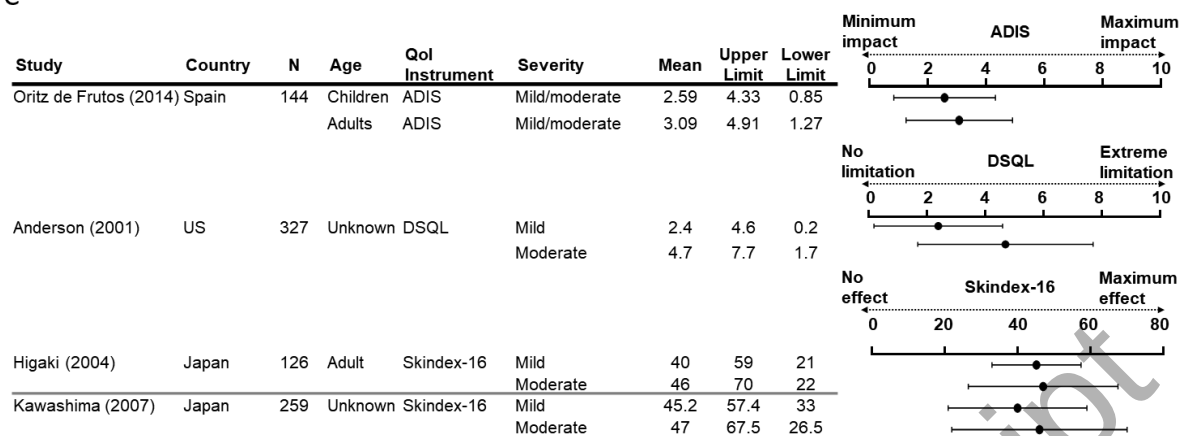
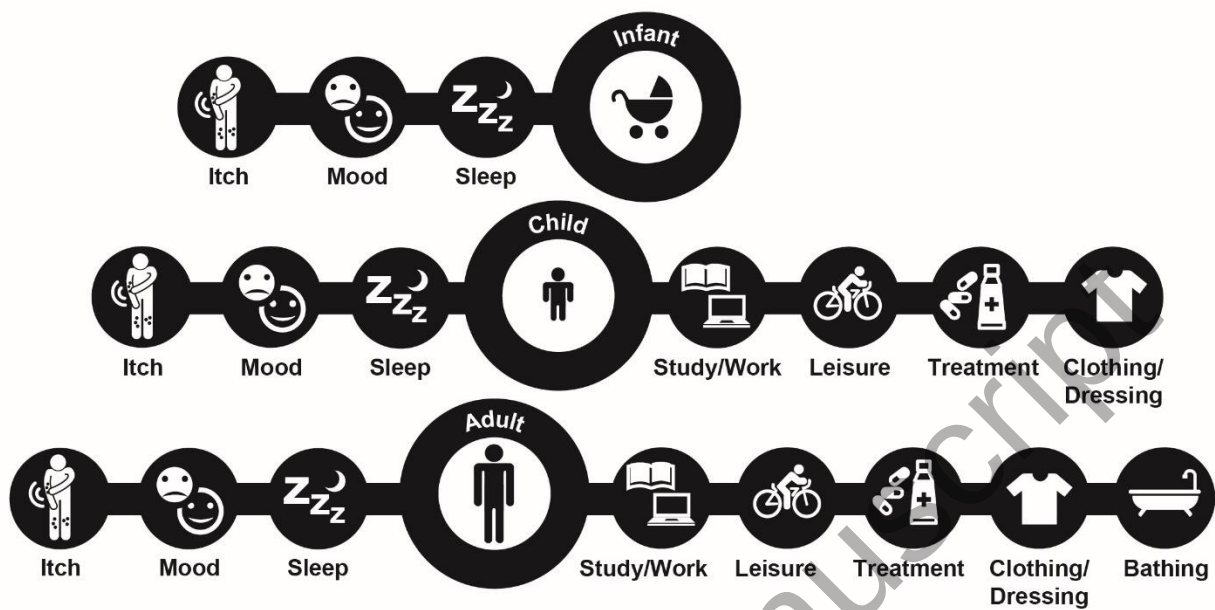


Figure 3.



Supplemental data.

Table S1. Search strategy for MEDLINE performed December 20, 2016.*

Search	Query	No. of records found
#1	dermatitis, atopic[MeSH Terms] OR 'atopic dermatitis'[tiab] OR 'atopic eczema'[tiab] OR 'infantile eczema'[tiab] OR 'pediatric eczema'[tiab]	22,798
#2	quality of life OR utility OR disutility OR activities of daily living OR patient burden OR patient-reported outcome OR PRO OR patient satisfaction OR patient preference OR patient withdrawal OR functioning OR symptom burden OR caregiver	1,010,135
#3	#1 AND #2	1610
#4	costs OR cost analysis OR cost-benefit analysis OR cost benefit OR budget impact OR health care costs OR healthcare costs OR cost of illness OR employer health cost OR health expenditures OR healthcare utilization OR economic burden OR absenteeism OR presenteeism OR productivity	813,655
#5	#1 AND #4	440
#6	#3 OR #5	1230 ^a

Abbreviations. MeSH, Medical Subject Heading; PRO, patient-reported outcome; tiab, title/abstract.

*Search limitations/filters applied to search 6 included date range = past 20 years; language = English; no animal studies; no narrative reviews.

Table S2. Search strategy for EMBASE performed December 20, 2016.*

Search	Query	No. of records found
#1	'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'atopic eczema':ab,ti OR 'infantile eczema':ab,ti OR 'pediatric eczema':ab,ti	37,117
#2	'quality of life'/exp OR 'quality of life' OR utility OR disutility OR 'activities of daily living'/exp OR 'activities of daily living' OR 'patient burden' OR 'patient reported outcomes'/exp OR 'patient reported outcomes' OR PRO OR 'patient satisfaction'/exp OR 'patient satisfaction' OR 'patient preference'/exp OR 'patient preference' OR 'patient withdrawal' OR functioning OR 'symptom burden'/exp OR 'symptom burden' OR 'caregiver'/exp OR caregiver	1,197,099
#3	#1 AND #2	3077
#4	costs OR 'cost analysis'/exp OR 'cost analysis' OR 'cost benefit analysis'/exp OR 'cost benefit analysis' OR 'cost benefit'/exp OR 'cost benefit' OR 'budget impact' OR 'health care costs'/exp OR 'health care costs' OR 'healthcare costs' OR 'cost of illness'/exp OR 'cost of illness' OR 'employer health cost' OR 'health expenditures'/exp OR 'health expenditures' OR 'healthcare utilization'/exp OR 'healthcare utilization' OR 'economic burden'/exp OR 'economic burden' OR 'absenteeism'/exp	548,089

	OR absenteeism OR 'presenteeism'/exp OR presenteeism OR 'productivity'/exp OR productivity	
#5	#1 AND #4	672
#6	#3 OR #5	1,804 ^a

Abbreviations. ab.ti, abstract title; exp, explode; PRO, patient-reported outcome.

*Search limitations/filters applied to search #6 included date range = past 20 years; language = English; human studies; no narrative reviews.

Table S3. Search strategy for the Cochrane Library performed December 20, 2016.*

Search	Query	No. of records found
#1	MeSH descriptor: [Dermatitis, Atopic] explode all trees	1,134
#2	'atopic dermatitis' or 'atopic eczema' or 'infantile eczema' or 'pediatric eczema':ti,ab,kw (word variations have been searched)	2,320
#3	#1 OR #2	2,452
#4	quality of life or utility or disutility or activities of daily living or patient burden or patient-reported outcome or PRO or patient satisfaction or patient preference or patient withdrawal or functioning or symptom burden or caregiver:ti,ab,kw (word variations have been searched)	194,076
#5	#3 AND #4	471
#6	costs or cost analysis or cost-benefit analysis or cost benefit or budget impact or health care costs or healthcare costs or cost of illness or employer health cost or health expenditures or healthcare utilization or economic burden or absenteeism or presenteeism or productivity:ti,ab,kw (word variations have been searched)	53,651
#7	#3 AND #6	79
#8	#5 OR #7	514
#9	#8 Publication year 1996-2016	463

Abbreviations. MeSH, Medical Subject Heading; PRO, patient-reported outcome; ti,ab,kw, title, abstract, keyword.

*Search limitations/filters applied included date range = past 20 years.

Table S4. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Population	Studies of at least 25* patients of any age with mild or moderate AD [†]	Studies of fewer than 25* patients with mild or moderate AD or studies evaluating only patients with severe AD
Interventions/ comparators	• Crisaborole • TCIs • TCS • Phototherapy • Systemic therapy	Studies without at least 1 of these interventions if interventions are disclosed (studies that do not specify interventions are included)
Outcomes	• Economic outcomes (direct and indirect costs, economic analyses) • PROs (HRQoL, caregiver burden)	Studies that do not report data for at least 1 of these outcomes
Study design	• Phase 2, 3, or 4 randomized controlled trials • Open-label trials; pragmatic trials • Single-arm trials • Prospective observational studies • Retrospective observational studies	• Phase 1 clinical trials • Pharmacokinetic/pharmacodynamics studies • Preclinical or animal studies • Guidelines • Editorials, letters, or commentaries

	and database studies • Registries and surveys • Case studies, reports, or series • Meta-analyses and systematic literature reviews[‡] • Health economic studies • Conference abstracts • Dissertations	• Narrative literature reviews
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Abbreviations. AD, atopic dermatitis; HRQoL, health-related quality of life; PRO, patient-reported outcome; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

* Sample size was tracked during screening.

[†] Although the primary focus was mild, mild to moderate, or moderate AD, studies that did not specify AD severity or studies of populations with mixed AD severity without appropriately stratified data were tracked separately during screening.

[‡] Reference lists from these types of studies were evaluated for potential additional studies for inclusion in the systematic literature review.

Table S5. QoL instruments used by studies in the systematic review.

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
Atopic Dermatitis Impact Scale	ADIS	Torrelo A et al. Eur J Dermatol 2012;22:97-105	Disease specific	Clinicians were asked about the following: • Severity of AD symptoms (3 items) • AD affectation: sleep disturbances (2 items), school/professional fulfillment (4 items), and emotional disturbances (10 items) • Attitude toward AD flares and topical pharmacologic treatment (4 items)	0 (minimum impact) to 10 (maximum impact)	Not specified

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
				- Overall satisfaction with topical pharmacologic treatment (1 item, visual analog scale [VAS]) - Perceived benefits of topical pharmacologic treatment for flares (6 items) Patients were asked about the following: - Attitude toward medical recommendations (hygienic and preventive strategies, 4 items) - Satisfaction with medical		

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
				recommendations for AD management and control (1 item, VAS) - Satisfaction with the information given by their specialist (1 item, VAS) - Feelings before the next flare (5 items)		
Children's Dermatology Life Quality Index	CDLQI	Lewis-Jones MS, Finlay AY. Br J Dermatol 1995;132:942-9	Dermatology specific	10 questions covering - Symptoms/feelings - Leisure - School/holidays - Personal relationships - Sleep	0 (no effect) to 30 (large effect)	1 week

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
				Treatment		
Dermatology Life Quality Index	DLQI	Finlay AY, Khan GK. Clin Exp Dermatol 1994;19;210-6	Dermatology specific	10 questions covering - Symptoms/feelings - Daily activities - Leisure - Work/school - Personal relationships - Treatment	0 (no effect) to 30 (large effect)	1 week
Dermatology- specific Quality of Life	DSQL	Anderson RT, Rajagopalan R. J Am Acad Dermatol 1997;37:41-50	Dermatology specific	52 questions over 7 domains: - Physical symptoms - Daily activities - Social activities - Work/school experiences - Self-perception	0 (no limitation) to 10 (extreme limitation)	1 month

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
				- SF-36 vitality subscale - SF-36 mental subscale		
EuroQoL 5 Dimensions	EQ-5D	EuroQoL Group. Health Policy 1990;16:199-208	General	5 dimensions - Mobility - Self-care - Usual activities - Pain/discomfort - Anxiety/depression	0 to 1 with 0 being full health	Status at time of completion
Infant's Dermatitis Quality of Life Index	IDQoL	Lewis-Jones MS et al. Br J Dermatol 2001;144:104-10	Dermatology	10 questions covering - Symptoms/feelings - Leisure - Family activities - Personal relationships - Sleep	0 (no effect) to 30 (large effect)	1 week

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
				Treatment		
12-Item Short-Form Health Survey	SF-12	Ware J Jr et al. Med Care 1996;34:220-33 www.sf-36.org	General	12 questions across 8 domains - Physical functioning - Role-physical - Bodily pain - General health - Vitality - Social functioning - Role-emotional - Mental health	0–100; lower scores have worse QoL	Standard: 4 weeks acute: 1 week
36-Item Short-Form Health Survey	SF-36	Ware JE Jr, Sherbourne CD. Med Care 1992;30:473-83	General	36 questions across 8 domains - Physical functioning - Role-physical problem - Bodily pain	0–100; lower scores have worse QoL	Standard: 4 weeks acute: 1 week

Name	Abbreviation	Reference	Type	Brief summary and domains	Score range	Recall period
		McHorney CA et al. Med Care 1993;31:247-63 www.sf-36.org		• General health • Vitality • Social functioning • Role-emotional • Mental health		
Skindex-16	None	Chren MM et al. J Cutan Med Surg 2001;5:105-10	Dermatology-specific	16 questions across 3 domains: • Emotions • Functioning • Symptoms	0 (never bothered) to 100 (always bothered)	1 week

Abbreviations. AD, atopic dermatitis; QoL, quality of life.

Table S4. Instruments to assess atopic dermatitis severity

Name	Abbreviation	Reference	Brief summary and domains	Score range
Eczema Area and Severity Index	EASI	Hanifin JM et al. Exp Dermatol 2001;10:11-8	- For age >8 years - Domains: erythema, induration/papulation, excoriation, and lichenification - Scored 0 (none) to 3 (severe) - Locations: head and neck, trunk, upper extremities, lower extremities - Extent of involvement scored as: 0 = none; 1 = <10%; 2 = <10%–29%; 3	0–72, tallied as sum of below values Head/neck: (Erythema+Induration/papulation+Excoriation+Lichenification)×Area×0.1 Upper limbs: (Erythema+Induration/papulation+Excoriation+Lichenification)×Area×0.2 Trunk: (Erythema+Induration/papulation+Excoriation+Lichenification)×Area×0.3 Lower limbs: (Erythema+Induration/papulation+Excoriation+Lichenification)×Area×0.4

Name	Abbreviation	Reference	Brief summary and domains	Score range
			= 30%–49%; 4 = <50%–69%; 5 = <70%–89%; 6 = >90%–100% Each location scored	
Investigator's Global Assessment	IGA	Futamura M et al. J Am Acad Dermatol 2016;74:288-94	- Multiple options; broadly defined as overall evaluation of AD severity using an ordinal scale or an ordered categorical variable that was scored using points by an investigator or a physician - FDA recommends IGA as primary end point for AD clinical trials	Depends on specific scale used

Name	Abbreviation	Reference	Brief summary and domains	Score range
Nottingham Eczema Severity Score	NESS	Emerson RM, Charman CR, Williams HC. Br J Dermatol 2000;142:288-97	• Specific to children • Domains: clinical course, disease intensity, and extent of BSA involvement • Graded from 1–5	Ranges from 3 to 15; sum of grades from clinical course + disease intensity + extent of BSA involvement
Rajka and Langeland	R&L	Rajka G, Langeland T. Acta Derm Venereol (Stockh) 1989;69 (suppl 144):13-4	• 3 domains: extent (childhood/adult and infant), course, and intensity • Grades from 1–3	Sum scores for 3 domains; ranges from 3 (mild) to 9 (severe)

Name	Abbreviation	Reference	Brief summary and domains	Score range
Severity Scoring of Atopic Dermatitis	SCORAD	European Task Force on Atopic Dermatitis. Dermatology. 1993;186:23-31	- Extent range from 0%–100% 6 intensity domains: erythema, edema/papulation, oozing/crusts, excoriations, lichenification, dryness ranged from 0 (absent) to 3 (severe) 2 subjective domains: pruritus, sleep loss graded using a VAS of 0–10	Range 0–103. Consists of Extent/5 + (7 × Intensity)/2 + Subjective
Six Area, Six Sign Atopic Dermatitis	SASSAD	Berth-Jones J. Br J Dermatol 1996;135(suppl 48):25-30	6 signs: erythema, exudation, excoriation, dryness, cracking, and lichenification 6 sites: arms, hands, legs,	0–108

Name	Abbreviation	Reference	Brief summary and domains	Score range
			feet, head and neck, and trunk Scored on scale of 0 (absent) to 3 (severe)	
Patient-Oriented Eczema Measure	POEM	Charman CR et al. Arch Dermatol 2004;140:1513-9	- Domains related to symptoms: itching, sleep disturbance, bleeding, weeping/oozing of the skin, dryness/roughness of the skin, flaking of the skin, and cracking of the skin - Responses to 7 questions regarding symptoms scored as follows: 0 = no days; 1 = 1–	0–28; total of scores from 7 symptom questions

Name	Abbreviation	Reference	Brief summary and domains	Score range
			2 days; 2 = 3–4 days; 3 = 5–6 days; 4 = every day	

Abbreviations. AD, atopic dermatitis; FDA, US Food and Drug Administration.