Title: Pruritus and Pain Constitute the Main Negative Impact of Atopic Dermatitis From the Patient's Perspective: A Systematic Review

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Abstract

Atopic dermatitis (AD) is an inflammatory skin disease characterized by intense itching and highly visible signs, representing a great burden to the patient. Despite its straightforward diagnosis, AD severity and burden can be underestimated in routine clinical practice. This review aims to determine the impact of AD on patients' lives, establish which domains of life are most affected, and identify symptom drivers of AD burden. A systematic literature review was conducted in Pubmed/Medline, Web of Science and Scopus following Cochrane and PRISMA recommendations. Observational studies published in English or Spanish between January 1st 2018 and August 31st 2022, evaluating the impact of AD and its symptoms from the patient's perspective were included. Reviewed studies were assessed for quality following the STROBE Checklist. A total of 28 observational studies evaluating the impact of AD and its symptoms from the patient's perspective were included in the review. All domains of the AD patient's life were found to be greatly affected, including health-related quality of life (HRQoL), emotional health, sleep disorders, work impairment, health-care resource utilization, cognitive function, and development of comorbidities. The more severe the disease, the greater the impact, worsening in patients with moderate and severe AD. Pruritus and pain are reported to be the disease symptoms with the greatest impact. In conclusion, AD impacts several domains of patients' lives, especially HRQoL and mental health. Pruritus and pain are identified as the main drivers of AD impact, suggesting that optimal symptom control may reduce the burden and improve disease management.

Capsule summary

- Atopic dermatitis (AD) and its symptoms affect all domains of patient's life
- Pruritus and pain are the main drivers of AD burden
- Controlling pruritus and pain in patients with AD may reduce disease burden posed on patients' quality of life

Introduction

Atopic dermatitis (AD) is a chronic relapsing-remitting disease, typically presenting dry skin, eczema, and pruritus. In the Western population, AD affects 10% to 15% of children and 2% to 10% of adults[1]. Clinically, there is a notable phenotypic variability driven by a complex underlying

multifactorial pathogenesis involving both genetic and environmental factors, which interact with the skin and the immune system, leading to a loss of skin barrier integrity, dysregulation of innate and adaptative immune responses, and dysbiosis of the skin microbiome[1-3]. The main AD symptoms (pruritus, pain, and sleep loss) and highly visible signs (e.g., redness, flaking, bleeding from scratching) can interfere with patient's daily life, impairing their psychosocial and work capacities, and worsening their health-related quality of life (HRQoL)[4-6]. In this regard, several authors have shown that more severe AD symptoms are associated with a higher negative impact on patients' lives[4,5,7].

Severity of AD can be assessed using different clinical measurement scales[8]. The Investigator Global Assessment (IGA), SCORing AD (SCORAD) index[9] and Eczema Area Severity Index (EASI)[10] have been validated for this purpose but their use in daily clinical practice may be limited since they can be time-consuming[8].

Alternatively, patient-reported outcome measures (PROMs) enable disease impacts to be evaluated in many domains from the patient's perspective, providing an important complement to clinical outcomes[11]. Currently, several validated PROMs are available, but most focus on the global HRQoL impairment rather than comprehensively evaluating the impact of the disease[12]. PROMs were originally developed for clinical trials[13]; consequently, the burden of AD has frequently been underestimated in routine practice[8,14]. However, the use of PROMs in routine clinical practice has been found valuable in assessing disease impact[11,15].

In view of all the above, we devised the present systematic review to gather and synthesize evidence for the impact of AD from the patient's perspective in clinical practice. Additionally, we aimed to determine which domains of the patient's life are most greatly affected by the disease and which disease symptoms have the strongest impact.

Methods

Search strategy

A literature search was conducted in September 2022 in the international databases Pubmed/Medline, Web of Science and Scopus following the Cochrane methodology[16]. Standardized search filters and free text of Medical Subject Heading terms were used when possible. This search was complemented by a manual search in grey literature search engines (i.e., Google Scholar; https://scholar.google.es/) and dermatitis-related websites such as the European Academy of Dermatology and Venereology (https://www.eadv.org/) or

the Harmonising Outcome Measures for Eczema (http://www.homeforeczema.org/index.aspx). Search terms and strategies followed for each database are shown in Supplementaty Table 1.

Eligibility criteria

Observational studies published between January 1st 2018 and August 31st 2022, evaluating the impact of AD and its symptoms from the patient's perspective were included. Only studies published in English and/or Spanish were selected.

Clinical trials, economic evaluations, opinion articles, letters to the editor, conference papers, narrative or systematic reviews, observational studies focused on a specific drug and its characteristics, and observational studies addressing the impact of AD from a perspective other than the patients' were excluded.

Study selection

Two independent researchers selected the studies following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[17]. Discrepancies were solved by consensus or through the involvement of a third team member.

Data extraction

Data were extracted by one researcher and validated by the other researcher. As previously stated, discrepancies were solved by consensus or through the involvement of a third team member.

The following variables were extracted from the selected studies: study design (case series/case study, cross-sectional, case-control, retrospective, prospective cohort), characteristics of the study population (sample size, type of population [adult, pediatric, and/or adolescent], mean age, gender, severity of the disease [severe, moderate, mild; tool to assess disease severity]), domains of patients' life affected by the disease, symptoms that have the greatest impact, study limitations, conclusions.

Quality assessment methodology

The quality of the observational studies reviewed was assessed according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) items[18]. Quality assessment data were extracted simultaneously with data related to the study.

Results

Articles selection

The literature search yielded 821 citations. Of these, 382 were eliminated as duplicates and 399 were discarded for failing to meet eligibility criteria or for not providing relevant information. After reviewing the full text of the remaining publications, a total of 28 publications were included in the systematic review (Figure 1).

Articles description

All publications included in the review were observational studies; 22 (78.6%) had a cross-sectional design, three (10.7%) prospective, two (7.1%) retrospective, and one (3.6%) prospective and cross-sectional (Table 1).

Quality assessment revealed that 11 publications (39.3%) met at least 80% of STROBE recommendations. Cross-sectional studies showed a variable percentage of well reported STROBE items, ranging from 55% to 91%. The prospective studies presented a high percentage (82-86%) of compliance with the recommendations, while one of the retrospective studies only reported half of the items appropriately.

Impact of AD on patients' lives

The main findings of the reviewed studies were grouped into eight categories according to the information provided regarding the impact of AD on patients' lives (Table 1): patients' HRQoL, emotional health, sleep disorders, work impairment, lifestyle and social activities, health-care resource utilization (HCRU), comorbidities, and cognitive function.

In each category, information was presented according to AD burden, burden across disease severity and impact of disease symptoms.

Patients' health-related quality of life

Twenty publications containing data about the impact of AD on patient's HRQoL were identified.

Ten studies[20,23,30-32,34,36,40,45,46] assessed AD burden in terms of patients' HRQoL, showing that AD impaired patients' HRQoL[20,23,30-32,40,45,46], affecting both their physical and mental health[20,23,40,46]. To studies[34,36] focused on AD impact on HRQoL according to skin lesion location. Both established that lesions in visible areas were associated with a lower HRQoL. One[36] of these studies also evaluated the impact of lesions in sensual areas, reporting that their presence negatively affected patients' HRQoL and increased disease burden.

Seven publications[20,22,26,35,39,40,45] evaluated the burden of AD according to disease severity with results showing discrepancies. Four studies[22,26,39,40] reported a significantly poorer HRQoL in patients with severe AD. Of these, one study[40] found a correlation between scores obtained in HRQoL questionnaires and Patient Oriented Eczema Measure (POEM) and Patient Oriented (PO)-SCORAD scores. Another publication[20] associated AD severity with mental and physical impairment. In contrast, three studies[20,35,45] did not find a statistically significant association between AD severity and patients' HRQoL.

Finally, nine studies[24,28-30,35,37,41,44,45] reported data on the burden of AD symptoms affecting HRQoL. Thus, more frequent and intense pruritus and/or pain were associated with a poorer HRQoL[24,28,29,35,37,41,44]. In addition, HRQoL impairment due to AD symptoms was associated with depression, sleep impairment, and suicidal ideation[30,35,45].

Emotional Health

Twelve publications reporting data about the impact of AD on emotional health were identified.

Nine studies[20,23,30-32,38,42,45,46] included data about the burden of AD on mental health, reporting increased depression and anxiety in patients with AD compared with controls. One of these studies[31] also showed that disease severity was associated with a higher prevalence of suicidal ideation in patients with AD compared with non-AD controls.

Eight studies[20,22,25,27,30,38,42,45] evaluated the emotional impact of AD according to disease severity, reporting contradictory results. Six studies[22,25,27,30,38,42] found a significant association between AD severity and a higher prevalence of depression and anxiety. In contrast, two studies[20,45] did not find significant differences between mild or mild/moderate and severe AD.

Lastly, three studies[30,42,45] assessed the emotional burden of AD symptoms. They showed that pruritus and sleep disturbance were correlated with a greater impact on patients' emotional health domains, such as anxiety and depression.

Sleep disorders

Nine of the reviewed publications[20,22,23,29,31,33,35,44,45] provided data about the impact of AD on sleep impairment and sleep disorders.

Four studies[20,23,29,31] reported data about the disease burden. Three studies[20,23,29] found a significantly higher percentage of AD patients with sleep disorders compared with controls, while the fourth[31] did not find any association between AD and sleep disturbance.

Five studies[20,22,29,33,35] evaluated the burden of AD across disease severity, with discrepancies in their results. Two studies[22,35] found a significantly positive correlation between AD severity and sleep impairment; hence, patients with moderate/severe AD reported more sleep impairment than those with mild AD. In contrast, three studies did not observe this correlation; one of the studies[20] did not find any significant differences in sleep disorders between patients with moderate/severe and mild forms of AD; one study[33] only found a significant association of sleep disturbance and AD in patients with severe or very severe AD; and finally, one study[29] did not find any correlation between AD severity and sleep disturbances in patients with AD.

Five studies[29,33,35,44,45] investigated the burden of disease symptoms. Three studies[29,33,45] found a significant correlation between pruritus and//or pain and sleep impairment. In contrast, one study[35] did not find this correlation. Finally, one qualitative study using focus groups and patient interviews[44] reported that pain was not always limited to one time of the day and, in particular, it could affect both the patient's and other family members' sleep.

Work impairment

Seven publications[19-24,37] reporting data on the impact of AD on work productivity were identified.

Two studies[20,23] provided data about the burden of AD. Neither one found significant differences between AD patients and controls regarding absenteeism. Overall, both studies found significant work impairment in AD patients compared with controls.

Four studies[19-22] evaluated the burden of AD according to disease severity, showing that the effect on work productivity was greater in patients with moderate/severe AD than in patients with mild AD. In addition, these authors determined that activity impairment worsened in parallel with AD severity.

Two studies[24,37] assessed the impact of AD symptoms. Both observed that pruritus and sleep disturbance were independently associated with work impairment in patients with AD. An

association was also established between pruritus severity and frequency and lower work productivity by one of the studies[37].

Lifestyle and social activities

Five publications[30,36,40,44,46] contained data on the impact of AD on lifestyle, social interaction, and sexual health of AD patients.

Three of these publications[30,40,46] reported data addressing the burden of AD. Of these, two studies[30,46] measured social interaction and isolation, finding that AD was not significantly associated with social isolation in AD patients compared with controls. In contrast, another study[40] showed that AD limited patients' lifestyles, causing them to avoid social interaction, and negatively impacting their social activities.

Two studies[36,40] assessed the burden of AD across disease severity. One study[36] showed that severe AD negatively impacted both patients' and their partners' sexual desire compared with mild AD. Similarly, the second study[40] showed that even patients with mild AD reported that AD impacted their lifestyle and daily activities; moreover, this impact was greater in patients with severe AD.

Finally, one study[44] reported that AD-associated pain affected patients' daily activities, including sexual relations.

Health-care resource utilization

Three studies[20,23,28] provided data about the impact of AD on HCRU.

Two studies[20,23] reported a higher frequency of visits to health-care providers, including visits to the Emergency Department, of AD patients compared with controls. In addition, they established that this frequency was even higher in patients with inadequate disease control, with these patients also reporting a higher number of hospitalizations[23].

One study[20] explored the HCRU across self-reported disease severity and found no significant differences between patients with moderate/severe AD and those with mild AD.

One study[28] evaluated the association between skin pain in patients AD with HCRU. The authors found that AD patients suffering from pain were more likely to request medical consultations with dermatologists or general practitioners.

Comorbidities

Two publications[20,22] evaluated the impact of AD on patients' comorbidities.

One of them[20] focused on the burden of AD, finding that AD patients presented a significantly higher self-reported prevalence of arthritis, asthma, nasal allergies/hay fever, high total cholesterol level, and osteoporosis/osteopenia compared with non-AD controls. These authors did not find statistically significant differences regarding the prevalence of diabetes or hypertension; nor did they report statistically significant differences in the prevalence of comorbidities according to AD severity.

In contrast, the other study[22] determined that the number of atopic comorbidities (asthma, food allergies and atopic keratoconjunctivitis) increased with AD severity; similarly, the proportion of patients with more than one comorbid non-atopic condition was higher among severe AD patients than mild or moderate sufferers.

None of the identified studies evaluated the burden of disease symptoms.

Cognitive function

Only one publication[43] evaluating the impact of AD on cognitive function was identified. This study showed that the cognitive function in AD patients was inversely associated with more severe disease and stronger symptoms (pruritus, sleep disturbance, pain).

Discussion

We systematically reviewed the impact of AD on different domains of patients' lives. A total of 28 observational studies were identified; HRQoL (n = 20) and emotional health (n = 12) were the most frequent domains explored, revealing the high burden of AD thereon. Regarding AD symptoms, pruritus (n = 12) and pain (n = 9) were those most commonly addressed in the reviewed studies, suggesting that these symptoms were the main drivers of AD burden.

The results of this systematic review confirm that AD has a strong impact on HRQoL, negatively affecting social functioning, emotional well-being, and occupational pursuits. Most studies report greater HRQoL impairment in patients with severe AD compared with mild or moderate AD. However, some authors did not detect differences across disease severity[20,35,45], suggesting that even patients with mild AD experience significantly poorer HRQoL. In line with these results, Balieva et al.[47] repored that patients with common skin diseases, such as AD, experience a substantial impairment of HRQoL compared with healthy controls. Such impairment is similar to the reduced HRQoL caused by diabetes mellitus, cardiovascular disease or some cancers, among others. In particular, AD patients have a lower mean global HRQoL,

fourfold increased OR for impairment in self-care, activity and pain/discomfort; and twofold risk for depression/anxiety.

Pruritus and pain are indicated as the main drivers of HRQoL impairment; however, the invisible nature of these symptoms can be challenging to evaluate and cannot be perceived directly by a physician[6]. Therefore, in clinical practice the relevance of pruritus and pain and their burden is frequently underestimated[6].

Pruritus is the hallmark of AD[48] and is reported as one of the most burdensome symptoms of this disease. In addition to strongly affecting HRQoL, pruritus negatively impacts work productivity and patients' physical and psychological functioning. Patients with AD report that pruritus is relieved by pain; therefore, scratching relieves itching, which could lead to a vicious itch-scratch cycle, aggravating the disease[48]. Thus, reducing these AD-specific symptoms might improve AD management and enhance the patient's HRQoL. In this context, a recently published systematic review reports that AD patients value treatments that rapidly relieve itching and burning, emphasizing that even though flares may not be fully resolved in the short-term, immediate relief from itching and burning is a patient priority[49]. Likewise, a study aiming to explore the patient's perspective on individual AD symptoms in determining treatment response, reveals that, from a patient's perspective, pruritus and pain are the most important items when assessing whether a treatment is effective[50].

The results of this review also show a significant correlation between pruritus and sleep disturbance[29,33,45]. Pruritus commonly worsens at night, favoring scratching and disrupting sleep. Indeed, a recent review reported that scratching in AD patients was significantly associated with nocturnal awakenings, sleep fragmentation, and reduced sleep efficiency[51]. In this context, three of the identified studies in the systematic review report that pruritus and sleep disturbance are correlated with emotional impact[30,42,45]. These results are consistent with a recently published study showing that insomnia in AD patients may lead to anxiety and depression[52].

The review outcomes indicate that AD, particularly pruritus and sleep disturbance, impair work productivity[24,37]. In this regard, it is well known that insufficient sleep and rest strongly affect work productivity[53]. Thus, reducing pruritus in patients with AD might result in better sleep quality and improved work productivity.

Taken together, these results confirm that AD is a disease with strong negative impacts on patients' lives, beyond skin involvement.

Overall, patients with AD, especially those with poorly controlled AD and skin pain, registered more frequent medical consultations and hospitalizations[20,23,28]. However, according to the studies reviewed herein, AD severity was not significantly related to HRCU. In this context, other studies have reported high indirect costs related to AD, such as the prescription of medication unrelated to AD or sick leave[54-56]. Consequently, better control of the disease and its symptoms would reduce the economic burden of AD.

In the reviewed publications, a higher prevalence of comorbidities such as arthritis, asthma, nasal allergies, high cholesterol, or osteoporosis/osteopenia was found in AD patients compared with controls[20,22]. Such conditions may lead to increased complexity of their management and, thereby a greater use of healthcare resources. Moreover, these potential comorbidities make treatment decision-making more challenging for clinicians[57].

This review has some limitations, most of which are related to the search strategy and selection criteria. Firstly, the literature search did not include all possible databases (e.g., Embase), which might imply an incompleteness of the results. Secondly, the search was limited to the studies published between January 2018 to August 2022. Thirdly, only publications in English and Spanish were included. Moreover, according to STROBE recommendations, the quality of the studies reviewed is moderate, mainly due to the study design (observational studies) and the literature search topic. Finally, available studies exploring some specific domains are limited; therefore, further studies on these particular domains would be necessary to draw more robust conclusions.

Conclusion

In conclusion, several domains of a patient's life are affected by AD, thus impairing their HRQoL. Pruritus and pain, both AD-specific symptoms, are the main drivers of the negative AD impacts. Thus, controlling these symptoms could help reduce the burden of the disease and optimize disease management.

Author Contributions

JCAH, JMC, AF, PH, JJPR, ESB, JFS, and FJOF contributed to the data interpretation and critical revision of the manuscript. OI contributed to the conception and project design, data interpretation, and critical revision of the manuscript. MC contributed to the conception and

project design, data acquisition and data analysis, and drafting of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Author contributions

J.C.A.-H., J.M.C., A.F., P.H., J.J.P.-R., E.S.-B., J.F.S., and F.J.O.d.F. contributed to data interpretation and critical revision of the article. O.I. contributed to the conception and project design, data interpretation, and critical revision of the article. M.C. contributed to the conception and project design, data acquisition and data analysis, and drafting of the article. All authors have read and agreed to the published version of the article.

Conflicts of interest

J.C.A.-H. has received consulting fees from Abbvie, Galderma, Sanofi, Leo-Pharma, Pfizer, and Lilly; payment or honoraria for lectures, presentations, speakers bureaus, article writing, or educational events from Abbvie, Sanofi, Leo-Pharma, Pfizer, and Lilly; payment for expert testimony from Abbvie, Galderma, Sanofi, Leo-Pharma, Pfizer, and Lilly; support for attending meetings and/or travel from UCB and Sanofi; and is member of the board of the Spanish Registry BIOBADATOP. J.M.C. has received consulting fees from Abbvie, Galderma, Sanofi, Leo-Pharma, Pfizer, and Lilly; payment or honoraria for lectures, presentations, speakers bureaus, article writing, or educational events from Abbvie, Sanofi, Leo-Pharma, Pfizer, and Lilly; payment for expert testimony from Abbvie, Galderma, Sanofi, Leo-Pharma, Pfizer, and Lilly; support for attending meetings and/or travel from UCB and Sanofi; and is member of the board of the Spanish Registry BIOBADATOP. A.F. has received consulting fees from Abbvie, Pfizer, and Sanofi-Avents; payment or honoraria for lectures, presentations, speakers bureaus, article writing, or educational events from Abbvie, Galderma, Leo-Pharma, Lilly, Pfizer, and Sanofi-Aventis; and is member of the board of the AEDV. P.H. declares no conflicts of interest that might be relevant to the contents of this article. J.J.P.-R. has received consulting fees from Abbvie, Janssen, Leo-Pharma, Novartis, Lilly, Novartis, Pfizer, Sanofi, and UCB; payment or honoraria for lectures, presentations, speakers bureaus, article writing, or educational events from Abbvie, Almirall, Galderma, Janssen, Gebro-Pharma, Leo-Pharma, Novartis, Lilly, Novartis, Pfizer, Sanofi, Incyte, and UCB; support for attending meetings and/or travel from Abbvie, Almirall, Galderma, Janssen, Gebro-Pharma, Leo-Pharma, Novartis, Lilly, Novartis, Pfizer, Sanofi, and UCB. E.S.-B. has

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Figure Legends

Figure 1. PRISMA diagram showing the study selection process

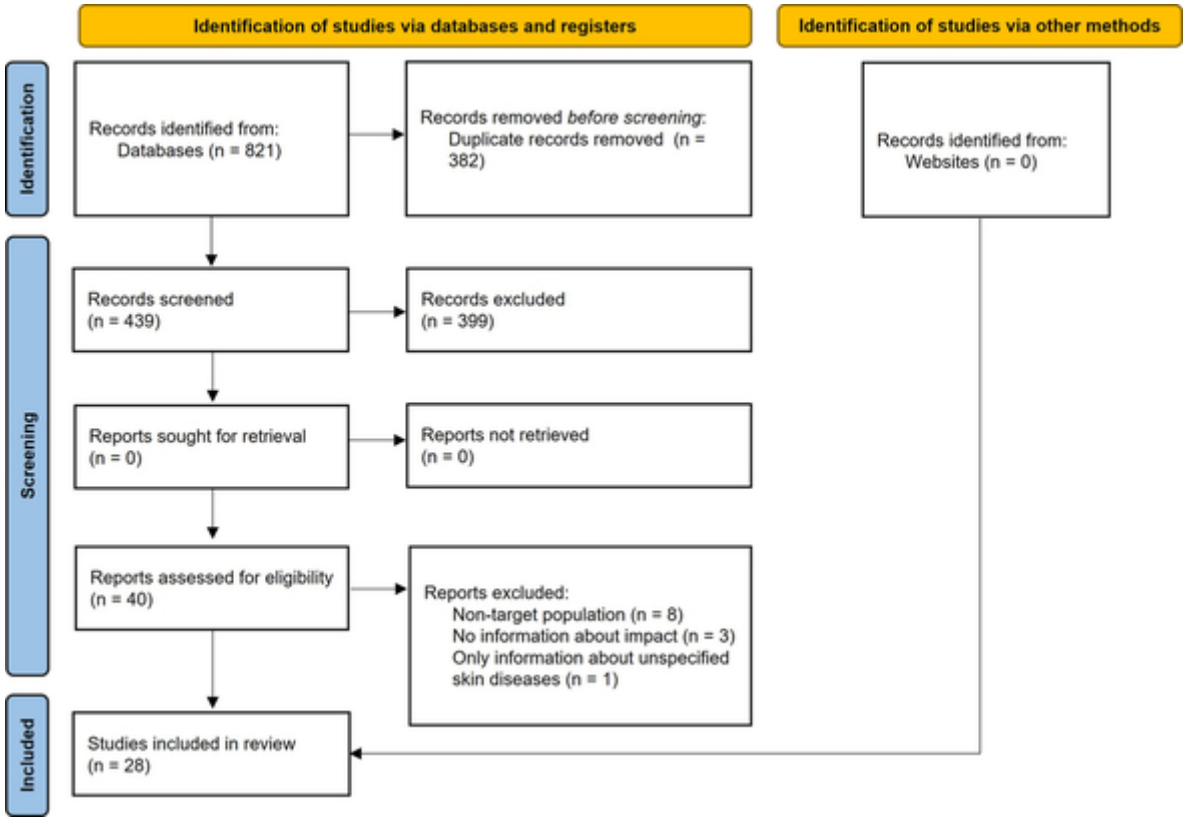
Identification of studies via databases and registers
Identification of studies via other methods
Identification
Records identified from:
Databases (n = 821)
Records removed *before screening*:
Duplicate records removed (n = 382)
Records identified from:
Websites (n = 0)
Screening
Records screened
(n = 439)
Records excluded
(n = 399)
Reports sought for retrieval
(n = 0)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 40)
Reports excluded:
Non-target population (n = 8)
No information about impact (n = 3)
Only information about unspecified skin diseases (n = 1)
Included
Studies included in review
(n = 28)

Table 1. Selected studies and main variables extracted

Reference	Study design	STROBE (max. 22)	Population size and subgroups	Affected domains	PROM	Main results
Andersen L, et al. 2020[19]	Cross-sectional	16	Population size: 1232 Subgroups: 134 mild; 825 moderate; 141 severe 1; 87 severe 2; 49 severe 3 measured with PO-SCORAD (<25 mild; 25-50 moderate; >50 severe)	Work impairment	WPAI	**Mild vs moderate vs severe[#]** **WPAI scores (mean ± SD)** **Absenteeism** Mild: 2.1 (10.1); moderate: 4.2 (14.0); severe: 10.3 (19.5) **Presenteeism** Mild: 4.0 (9.7); moderate: 22.0 (23.6); severe: 43.4 (28.5) **Overall work impairment** Mild: 6.0 (13.8); moderate: 24.1 (26.4); severe: 47.5 (29.7) **Activity impairment** Mild: 8.6 (14.8); moderate: 25.5 (24.6); severe: 52.4 (27.0)
Arima K, et al. 2018[20]	Retrospective	11	Population size: 1902 Subgroups: 1268 non-AD 634 AD (290; 45.45% moderate/ severe, 348 54.54% mild) self-rated by the question*: "How severe is your dermatitis/eczema? "*	Work impairment, comorbidities, emotional health, HRQoL, sleep disorders, HCRU	SF-36, WPAI, ad-hoc questions, self-reported	**AD vs control** **Comorbidities** Arthritis: 3.79 vs 0.87%, p< 0.001; asthma: 12.62 vs 2.44, p<0.001; nasal allergies/hay fever: 36.91 vs 14.83%, p<0.001; high cholesterol: 8.99 vs 4.26%. p<0.001; osteoporosis/osteopenia: 1.42 vs 0.47%, p<0.001 **Mood and sleep disorders** Depression: 10.25% vs 4.25%, p<0.001; sleep disorders: 12.93% vs 4.57%, p<0.001; anxiety: 3.31% vs 1.03%, p<0.001 **Health-related quality of life** SF-36 PCS: 42.29 vs 46.05, p< 0.001; SF-36 MCS: 52.04 vs 54.12, p<0.001; SF-6D: 0.71 vs 0.76, p<0.001 **Work productivity and activity** Absenteeism: 4.01 vs 3.54 (WPAI score); presenteeism: 28.63% vs 22.37%; p<0.001; overall impairment: 30.61% vs 24.62%, p<0.001; activity impairment: 32.18% vs 24.72, p<0.001 **Health-care resource utilization** Mean (SD) numbers of visits to health-care providers: 8.06 (16.90) vs 3.05 (6.27), p<0.001

						<u>Disease burden according to severity</u> **Comorbidities** No significant differences in the self-reported prevalence of comorbidities according to severity **Mood and sleep disorders** No significant differences according to severity **HRQoL** MCS, PCS and SF-36 scores were numerically lower for moderate/severe AD patients vs mild; no statistical significance **Work productivity and activity** Presenteeism: Mild: 26.10% vs Moderate/severe: 32.17%; p=0.018 Overall Work Impairment: Mild: 28.08% vs Moderate/severe: 33.79%; p=0.040 Activity impairment: Mild: 30.06% Moderate/severe: 35.14% p=0.023 **HCRU** No significant differences according to severity
Chan T, et al. 2021[21]	Cross-sectional	15	Population size: 200 Subgroups: 70 mild 72 moderate 58 severe based on SCORAD specialist measure	Work impairment	WPAI	**<u>Mild vs moderate vs severe</u>** **WPAI scores (mean ± SD)** **Absenteeism** Mild: 1.8 (1.3); moderate: 6.3 (2.7); severe: 5.6 (3.3) **Presenteeism** Mild: 23.7 (13.6); moderate: 42.1 (10.3); severe: 63.1 (9.0) **Work impairment** Mild: 24.7 (13.1); moderate: 44.8 (10.1); severe: 65.0 (7.8) **Activity impairment:** Mild: 29.9 (10.1); moderate: 44.7 (9.6); severe: 61.2 (8.7) All p values <0.001
de Bruin-Weller M, et al. 2020[22]	Cross-sectional	16	Population size: 1467 Subgroups:	Work impairment, comorbidities, emotional health, HRQoL, sleep disorders	DLQI, HADS, sleep VAS PO-SCORAD, PSQI, ad-	**<u>Mild vs moderate vs severe</u>** **Atopic comorbidities (%)** Asthma: 20.3 mild vs 31.7 moderate vs 43.5 severe, p<0.001; food allergy: 10.1 mild, p<0.001 vs 18.8 moderate, p<0.05 vs 25.3 severe;

			547 mild 520 moderate 400 severe, based on IGA		hoc question	atopic keratoconjunctivitis: 0.4 mild, p<0.001 vs 1.0, p<0.05 vs 2.3 severe) The proportion of participants with ≥1 comorbid atopic condition was higher among patients with severe AD (80.5%) compared with mild (58.9%, p<0.001) and moderate (74.6%, p<0.05) **Non-atopic comorbidities (%)** Cardiovascular: 8.4 vs 10.8 vs 15; musculoskeletal: 6.2 vs 7.1 vs 8.8; endocrine: 7.5 vs 10.0 vs 11.0; renal conditions: 1.8 vs 2.7 vs 2.3; mental conditions: 41.7 mild, p<0.001 vs 46.7 moderate, p<0.05 vs 54.3 severe The proportion of participants with ≥1 comorbid non-atopic condition was higher among patients with severe AD (54.3%) compared with mild (41.7%, p<0.001) and moderate (46.7%, p<0.05) **HADS scale score (mean ± SD)** Anxiety: 5.5 (4.0) mild vs 7.3 (4.2) moderate vs 9.4 (4.1) severe, p<0.001; depression: 3.8 (3.7) mild vs 5.5 (3.9) moderate vs 8.2 (4.4) severity, p<0.001 **Productivity last 4 weeks** At least one day missed: 33.3% mild, p<0.001 vs 52.4% moderate, p<0.05 vs 62.9% severe **DLQI scale score (mean ± SD)** HRQoL: 5.5 (4.9) mild vs 10.5 (6.3) moderate vs 1.2 (6.9) severe, p<0.001 **Pain NRS Scale (mean score; 1-10)** Mild: 1.7; moderate: 3.0; severe: 4.5; p<0.001 **Pruritus NRS Scale (score mean; 1-10)** Mild: 3.5; moderate: 5.3; severe: 4.1; p<0.001 **PO-SCORAD Itch VAS Scale (score mean; 1-10)** Mild: 3.8; moderate: 5.6; severe: 7.3; p<0.001 **Sleep disturbances (score mean; 1-10)** Mild: 2.0; moderate: 3.6; severe: 5.5; p<0.001

Eckert L, et al. 2020[23]	Cross-sectional	16	Population size: 1860 Subgroups: 58 inadequately controlled AD (DLQI >10) 383 controlled AD (DLQI<10) 1419 patients undetermined	Work impairment, emotional health, HRQoL, sleep disorders, HCRU	DLQI, SF-36, WPAI, self-reported	**<u>AD and IC-AD vs control</u>** **Emotional impairment** Depression: 25.8% and 36.2% vs 12.9%, p<0.001; anxiety: 31.9% and 51.7% vs 14.4%, p<0.001; sleep disorders: 22.7% and 39.7% vs 12.6%, p<0.001 **HRQoL** SF-36v2 PCS: 49.41 and 43.87 vs 51.15, p<0.001; SF-36v2 MCS: 41.96 and 34.78 vs 44.23, p<0.001 **Work Impairment** Presenteeism: 24.7% and 53.5% vs 21.2%, p=0.002 and p<0.001, respectively; overall work impairment: 27.0% and 57.1% vs 23.7%, p=0.009 and p<0.001, respectively; activity impairment: 31.8% and 51.7% vs 26.5%, both p<0.001; absenteeism: 8.69% and 12.84 vs 9.00%, p=0.745 and p=0.314, respectively **Health-care resource utilization** Mean (SD) number of visits: 7.4 (11.2) and 13.9 (17.8;) vs 4.5 (7.2), p<0.001 for both comparisons
Egeberg A, et al. 2021[24]	Cross-sectional	14	Population size: 631 Subgroups: All moderate/severe patients defined as an IGA score >3, EASI score >6 or treatment with biologic agent or immunosuppressant	Work impairment, HRQoL	DLQI, EQ-5D, WPAI	**HRQoL related to** **Pruritus** EQ-5D-3L from "all the time" to "rarely": 0.46 vs 0.94, p<0.05; DLQI "all the time" to "rarely": 14.32 vs 2.25, p<0.05 **Sleep disruption** EQ-5D-3L from "all the time" to "rarely": 0.65 vs 0.96, p<0.05; DLQI from "all the time" to “regularly”, “sometimes” and "rarely": 20.58 vs 12.77 vs 9.07 vs 6.42, p<0.05 **Anxiety** EQ-5D-3L from "sometimes" to " all the time": 0.83 vs 0.67, p<0.05; DLQI from "rarely" to "all the time": 6.92 vs 12.87, p<0.05 **Depression** EQ-5D-3L from "all the time" to "rarely": 0.40 vs 0.82, p<0.05; DLQI from "all the time" to "rarely": 21.55 vs 7.86, p<0.05 **Work productivity related to pruritus** **Absenteeism** WPAI scores from "all the time" to "rarely": 31.86 vs 4.19, p<0.05 **Presenteeism**

						WPAI scores from "rarely" to "all the time": 11.55 vs 33.20, p<0.05 **Work impairment** WPAI scores from "rarely" to "all the time": 10.63 vs 32.62, p<0.05 **Activity impairment** WPAI scores from "all the time" to “regularly”, “sometimes” and "rarely": 45.70 vs 36.65 vs 28.94 vs 8.84, p<0.05 **Work productivity related to sleep disruption** **Absenteeism** WPAI scores from "all the time" to “regularly”, “sometimes” and "rarely": 72.42 vs 27.34 vs 10.96 vs 0.19, p<0,05 **Presenteeism** WPAI scores from "rarely" to "all the time": 10.66 vs 42.02, p<0,05 **Work impairment** WPAI scores from "rarely" to "all the time". 8.03 vs 47.61, p<0,05 **Activity impairment** WPAI scores from "all the time" to “regularly”, “sometimes” and "rarely": 62.24 vs 44.88 vs 33.52 vs 14,57, p<0,05 **Work productivity related to depression** **Absenteeism** WPAI scores from "all the time" to “regularly”, “sometimes” and "rarely": 50.64 vs 50.83 vs 23.06 vs 1,23 **Presenteeism** WPAI scores from "sometimes" and "regularly" to "all the time": 38.14 vs 42.34 vs 2.12, p<0.05 **Work impairment** WPAI scores from "sometimes" and "regularly" to "all the time": 43.25 vs 52.38 vs 2.02, p<0.05 **Activity impairment** WPAI scores from "all the time" to “regularly”, “sometimes” and "rarely": 56.52 vs 51.52 vs 35.94 vs 23.95, p<0.05
Ferrucci S, et al. 2021[25]	Cross-sectional	15	Population size: 300 Subgroups: All moderate-to-severe AD patients	Emotional health	HADS	**Depression and anxiety** 44.6% and 53.0% of patients presented clinically significant depression and anxiety, respectively. Results show a relationship between depression or anxiety and each other (p<0.01). Depression is also related to disease severity with a beta of 0.09 (p<0.06) and

						poorer quality of life, measured by DLQI (beta=0.18; p<0.01). Anxiety is also related to poor sleep quality (SQ-NRS, b=0.11; p=0.03), poorer quality of life (b=0.10; p<0.01), disease severity (POEM; b=0.20; p<0.01; IGA; b=0.09; p=0.06), severity of itch (I-NRS; b=0.11; p=0.03). OR of severity of anxiety (1.51; p<0.01) and poor quality of life (1.06; p=0.04) are associated with significantly relevant depression symptoms. OR of severity of depression (1.51; p<0.01) are associated with significantly relevant anxiety symptoms.
Hsieh B, et al. 2020[26]	Cross-sectional	15	Population size: 200 Subgroups: 70 mild 72 moderate 58 severe based on SCORAD patient measure	HRQoL	DLQI, EQ-5D	**<u>Mild vs moderate vs severe</u>** **DLQI scores (mean ± SD)** Mild: 7.2 (3.7); moderate: 11.9 (4.4); severe: 18.5 (4.3) SCORAD and DLQI showed a positive correlation (Spearman's r=0.77, p<0.001) **EQ-5D** Patients with greater AD severity had more problems with mobility, usual activity, pain/discomfort, and anxiety/ depression, while self-care was not related to AD severity SCORAD and EQ-5D showed a negative correlation (Spearman's r=-0.46, p<0.001)
Hsu C, et al. 2022[27]	Cross-sectional	18	Population size: 200 Subgroups: N/A	Emotional health	HADS	**<u>Mild vs moderate vs severe</u>** **HADS-T (>14)** Mild: 34.3%; moderate: 62.5%; severe: 89.7% **HADS-A (>8)** Mild: 47.1%; moderate: 66.7%; severe: 91.4% **HADS-D (>8)** Mild: 15.7%; moderate: 26.4%; severe: 46.6% More cases with borderline score in both HADS-A and HADS-D in patients with moderate-to-severe than with mild AD (p<0.001)
Huet F, et al. 2020[28]	Cross-sectional	16	Population size: 5000 Subgroups:	HRQoL, HCRU	DLQI, SF-12	**<u>AD vs control</u>** **HRQoL**

			185 AD 4815 non-AD			Skin pain: 54.6% vs 6.0%, p<0.0001; Neuropathic component of pain: 73.6% vs 48.2%, p<0.002; MCS-12: 37.7 vs 42.3, p<0.001; DLQI scores: 15.2 vs 8.8, p<0.00001 **HRCU** Patients with AD and skin pain had more frequent consultations with dermatologists: OR 3.69 (95% CI 2.60–7.80), p<0.001
Kaaz K, et al. 2019[29]	Cross-sectional	16	Population size: 250 Subgroups: 100 AD 100 Psoriasis 50 Control	HRQoL, sleep disorders	AIS, DLQI, PSQI	**AD vs control** **Sleep disorders** AIS score (mean ± SD): 10.5 (5.5) vs. 5.5 (3.4), p<0.0001 PSQI score (mean ± SD): 8.3 (4.2) vs 3.1 (1.9), p<0.0001 **Prevalence of itch** None: 0%; mild: 14%; moderate: 26%; severe: 60%[#] **Prevalence of pain** None: 66%; mild: 11%; moderate: 10%; severe: 13%[#] **HRQoL** Itch and pain intensity impacted independently on DLQI: Itch: r=0.45, p<0.0001 Pain: r=0.36, p=0.026 **Disease burden according to severity** Severity of itch (VASmean) correlated with AIS (r=0.44, p<0.0001), but not with PSQI (r=0.21, p=0.09)
Kage P, et al 2021[30]	Prospective	18	Population size: 245 Subgroups: 161 non-AD 84 AD	Emotional health, HRQoL, lifestyle and social activities	CES-D, DLQI, GAD-7, HADS, LSNS-6, ad-hoc questions	**AD vs control** **CES-D (median [interquartile range]** 18 (10-27.8) vs 9 (5-8), p<0.001 **GAD-7 (median [interquartile range]** 6 (3-12.75) vs 2 (1-5), p<0.001 **LSNS-6 (median [interquartile range])** 18 (12-21) vs 19 (14.3-22), p=0.067 **DLQI (suicidal ideation vs non-suicidal ideation)** 17.0 (9.5-22.5) vs 8.0 (3-14), p=0.004

						<u>Disease burden according to severity</u> Within the group of AD patients, there was a significant correlation between the subjective skin severity with the depression and anxiety values: POEM significantly correlated with GAD-7 and CES-D with medium effect size r=0.468 and r=0.460, respectively, p<0.001. PO-SCORAD significantly correlated with GAD-7 and CES-D with weak effect size: r=0.325 and r=0.297, respectively, p<0.05. The EASI correlated neither with HADS-A nor -D nor with CES-D. **<u>Symptoms burden</u>** Sleep disturbance significantly correlated with medium effect size with GAD7 (r=0.460) and CES-D (r=0.447), p<0.05. Pruritus showed a significant correlation with GAD-7 and CES-D, but with weak effect size r=0.306 and r=0.263, respectively, p<0.05
Lee S, et al. 2018[31]	Cross-sectional	20	Population size: 37,578 Subgroups: 677 AD 36,901 non-AD	Emotional health, HRQoL, sleep disorders	EQ-5D, ad-hoc questions	**<u>AD vs control</u>** **Emotional health** Severe psychological stress: 31.1% vs 23.0%, p<0.001; depressed mood: 18.1% vs 13.1%, p=0.001; use of psychological counselling services: 4.7% vs 2.4%, p=0.001; depression: 18.4% vs 12.9%, p=0.002; suicidal ideation: 19.7% vs 13.3%, p<0.001 **Sleep impairment** Sleep duration did not differ between the two groups (p=0.068) **HRQoL** EQ-5D pain/discomfort: 27.1% vs 21.5%, p=0.003 EQ-5D anxiety/ depression: 16.0% vs 10.9%, p<0.001 EQ-VAS scores: 71.8 vs 74.3, p=0.004
Lee G, et al. 2022[32]	Cross-sectional	20	Population size: 16,304 Subgroups: 446 AD 13,022 non-AD	Emotional health, HRQoL	Ad-hoc questions, self-reported	**<u>AD vs control</u>** **Emotional health** Psychological stress: 34.78% vs 32.04%, p=0.31; experience of psychological consultation: 3.64% vs 2.97%, p=0.47; diagnosis of depression: 3.86% vs 2.82%, p=0.25 **HRQoL**

			2,836 other pathologies			Severe problems in mobility: 0.61% vs 0.15% p=0.03; pain/discomfort: 1.82% vs 0.59%, p<0.01; anxiety/depression: 0.68% vs 0.38%, p=0.32
Li J, et al. 2018[33]	Cross-sectional	17	Population size: 287 Subgroups: N/A	Sleep disorders	PROMIS SD and SRI	**PROMIS SD according to:** **POEM (none, mild, moderate, severe)**[#] Clear/mild: 80.95%, 19.5%, 0%, 0% Moderate: 78.89%, 20%, 1.11%, 0% Severe: 73.45%, 25.66%, 0.88%, 0% Very severe: 69.23%, 26.92%, 3.85%, 0% **Self-reported severity (none, mild, moderate, severe)**[#] Mild: 84.62%, 11.54%, 0%, 0% Moderate:75%, 23.33%, 1.67%, 0% Severe: 72.87%, 25.58%, 1.55%, 0% **VAS-Itch (none, mild, moderate, severe)**[#] Mild: 83.78%, 16.22%, 0%, 0% Moderate: 73.21%, 25.89%, 0.69%, 0% Severe: 75%, 21.25%,.75%, 0% Very severe: 65.52%, 34.48%, 0%, 0% **SA-EASI (none, mild, moderate, severe)**[#] 1: 82.81%, 15.63%, 1.56%, 0% 2: 74.6%, 23.81%, 1.59%, 0% 3: 69.84%, 28.57%, 1.59%, 0% **PROMIS SRI according to:** **POEM (none, mild, moderate, severe)**[#] Clear/mild: 76.19%, 9.52%, 9.52%, 4.76% Moderate: 67.78%, 21.11%, 8.89%, 2.22% Severe: 46.9%, 16.81%, 31.86%, 4.42% Very severe: 34.62%, 17.31%, 25%, 23.08% **Self-reported severity (none, mild, moderate, severe)**[#] Mild: 35.38%, 15.38%, 15.38%, 3.85% Moderate: 62.5%, 15%, 19.17%, 3.33% Severe: 43.41%, 20.16%, 24.03%, 12.4% **VAS-Itch (none, mild, moderate, severe)**[#] Mild: 67.57%, 18.92%, 10.81%, 2.7% Moderate: 61.61%, 14.29%, 22.32%, 1.79% Severe: 37.5%, 22.5%, 31.25%, 8.75%

						Very severe: 44.83%, 17.24%, 10.34%, 27.59% **SA-EASI (none, mild, moderate, severe)**[#] 1: 64.06%, 18.75%, 15.63%, 1.65% 2: 50.79%, 20.63%, 20.63%, 7.94% 3: 41.27%, 17.46%, 25.4%, 15.87% **<u>Disease burden according to severity</u>** Only a subset of subjects with severe or very severe POEM, moderate and severe self-reported global assessment of AD, severe or very severe VAS-itch, and highest tertile SA-EASI scores had significantly higher OR for all of aspects of SD and SRI ($p<0.05$)
Lio PA, et al. 2020[34]	Cross-sectional	18	Population size: 599 Subgroups: 254 mild 309 moderate 36 severe	HRQoL	DLQI, EQ-5D, ad-hoc question	**Correlation between location and HRQoL (DLQI, EQ-5D-3L, EQ-5D VAS, POEM)** Mean: 6.8 (5.6), 0.9 (0.1), 81.5 (16.3), 9.4 (6.9) Head and neck: 7.11 (0.62), 0.89* (-0.02), 78.6* (-4.2), 10.9* (2.3) Upper extremities: 7.05 (0.89), 0.90* (-0.02), 80.8* (-3.4), 10.1* (2.55) Lower extremities: 7.21 (1.16)*, 0.89* (-0.02), 80.2* (-2.8), 10.0* (1.99) Front: 7.85 (1.29)*, 0.90 (0.0001), 81.0 (0.64), 9.83 (0.63) Back: 7.13 (0.45), 0.89* (-0.03), 79.6 (-2.9), 10.1 (1.44) Face: 7.79 (1.47), 0.88 (-0.02), 75.9* (-6.1), 11.7* (2.91) Hands/fingers: 7.74* (1.24), 0.89* (-0.02), 80.4 (-1.9), 11.6* (3.51) Pelvis/genital: 9.43 (1.21), 0.73* (-0.17), 68.7* (-12), 11.9 (1.06) Feet/toes: 8.35 (0.96), 0.86* (-0.05), 78.8 (-1.0), 11.5 (1.20) *Significant differences ($p<0.0334$)
Mann C, et al. 2020[35]	Cross-sectional	18	Population size: 61 Subgroups: 25 AD 36 urticaria	HRQoL, sleep disorders	DLQI, ISI	**Disease burden (mean ± SD [range])** ISI-no flare: 8.7 ± 5.6 (0-23) ISI-flare: 16.0 ± 6.4 (2-27) *ISI scores have a maximum of 28* DLQI: 14.0 ± 8.7 (1-28) Pruritus VAS scale: 6.9 ± 1.9 (2-9) No correlation found between pruritus and ISI **HRQoL**

						Correlation between pruritus and DLQI: r=0.463, p=0.02 **<u>Disease burden according to severity</u>** No statistically significant differences between disease severity (EASI) and quality of life (DLQI). However, there was a significant correlation between disease severity (EASI) and sleep-impairment global score (r=0.43, p=0.032) and with the specific item "difficulty staying asleep" (r=0.487, p=0.014)
Misery L, et al. 2019[36]	Prospective and cross-sectional	19	Population size: 1024 Subgroups: 283 mild 414 moderate 327 severe (PO-SCORAD)	HRQoL, lifestyle and social activities	ABS-A, DLQI, EQ-5D, SF-12, ad-hoc questions	**HRQoL (visible area involvement vs without) (mean ± SD)** ABS-A: 29.0 ± 20.6 vs 14.9 ± 18.8, p<0.0001; DLQI: 10.4 ± 7.5 vs 6.1 ± 7.7, p<0.0001; EQ-5D: 0.68 ± 0.28 vs 0.70 ± 0.32, p<0.05; SF-12 MCS: 39.4 ± 10.1 vs 43.8 ± 9.3, p<0.0001 Involvement of sensual area ABS-A: 38.2 ± 19.5 vs 20.7 ± 19.4, p<0.0001; DLQI: 13.9 ± 7.1 vs 7.6 ± 7.2, p<0.0001; EQ-5D: 0.64 ± 0.31 vs 0.71 ± 0.28, p=0.0005; EQ5D-VAS: 60.2 ± 21.9 vs 64.9 ± 22.1, p<0.0001; SF-12 MCS: 37.0 ± 9.3 vs 41.8 ± 10.1, p<0.0001 Genital involvement ABS-A: 39.4 ± 19.5 vs 23.7 ± 19.4, p<0.001; DLQI: 8.9 ± 7.1 vs 4.5 ± 7.2, p<0.001; EQ5D-VAS: 58.5 ± 21.2 vs 63.2 ± 22.3, p<0.001; SF-12 MCS: 36.5 ± 9.1 vs 40.9 ± 10.2, p<0.001 **<u>Disease burden according to severity</u>** **Mild vs severe (PO-SCORAD)** Impact on sexual desire: 1.8% vs 9.5%, p<0.0001 Impact on partner's sexual desire: 0.7% vs 4.3%, p<0.0001

Murota H, et al. 2021[37]	Cross-sectional	17	Population size: 370 Subgroups: 141 mild pruritus 117 moderate pruritus 112 severe pruritus assessed with WP-NRS from 0-3 (mild), 4-6 (moderate) and 7-10 (severe)	Work impairment, HRQoL	DLQI, WPAI	**<u>Mild vs moderate vs severe</u>** **Work impairment** Mild: 5.2% (12.4); moderate: 21.7% (20.3); severe: 38.1% (26.2) **Quality of life (DLQI scores)** Mild: 1.8; moderate: 4.2; severe: 8.1 **Impact on sleep (Aderm-IS scores)** Mild: 1.6 (3.6); moderate: 6.6 (6.1); severe: 12.9 (7.8) **Impact on daily activity (Aderm-IS scores)** Mild: 1.6 (3.5); moderate: 6.4 (6.4);severe: 11.0 (9.0) **Impact on emotional state (Aderm-IS scores)** Mild: 1.9 (3.8); moderate: 7.0 (6.2); severe: 13.5 (9.3) *All data set a p-value <0,001, suggesting statical significance between pruritus severity using "mild" as a reference.*
Schonmann Y, et al. 2020[38]	Retrospective	20	Population size: 3,095,838 Subgroups: Depression cohort: 1,588,277 non-AD 392,433 AD Anxiety cohort 1,827,908 non-AD 426,430 AD	Emotional health	Diagnoses reported in primary care electronic health records	**<u>AD vs control</u>** Depression: HR 1.14-fold (99% CI, 1.12-1.16) Anxiety: HR 1.17-fold (99% CI, 1.14-1.19) **<u>Disease burden according to severity</u>** Regardless of atopic eczema severity, there was an association between atopic eczema with both depression and anxiety: compared to subjects without atopic eczema: the more severe the atopic eczema, the greater the risk of depression (p<0.0001)
Schwartzman G, et al. 2022[39]	Prospective	19	Population size: 955 Subgroups: N/A	HRQoL	PHQ-9, mEQ-5D, PGH	**Burden across severity:** In a multivariate linear regression model PGH-P4 T and mEQ-5D scores were inversely associated with patient-reported global AD severity, POEM, EASI, objective SCORAD, IGA, NRS average and worst itch, and PROMIS SRI and sleep disturbance, all with stepwise decreases in physical health with worsening severity (all p<0.05 in severe/very severe AD). PGH-M4 T scores were similarly inversely associated with all severity measures of AD and itch, PROMIS SRI and PHQ-9, with stepwise decreases of mental health with worsening severity (all p<0.05 in severe/very severe AD), but not with PROMIS sleep disturbance. AD severity had significant clinical associations with mental and physical HRQoL impairment in adults with AD. More severe disease was strongly associated with worse HRQoL scores

Silverberg J, et al. 2018[40]	Cross-sectional	17	Population size: 1787 Subgroups: 1185 non-AD 602 AD (289 mild, 175 moderate and 34 severe); self-reported by the patients asking the question: *Would you describe your AD or eczema as mild, moderate, or severe?*	HRQoL, lifestyle and social activities	DLQI, SF-12, ad-hoc questions	**<u>AD vs control</u>** **HRQoL** Fair or poor overall health: 25.8% vs 15.8%, p<0,0001; being somewhat or very dissatisfied with life: 16.7% vs 11.4%, p<0.05 SF-12 MCS: 45.9 vs 50.9, p<0.0001; SF-12 PCS: 53.0 vs 53.5, p<0.0001; DLQI: 4.9 vs 1.1, p<0.0001 Burden across disease severity: More severe AD was associated with even stronger effects on health rating and life satisfaction. In particular, 35.0% and 31.6% of patients with self-reported severe AD reported only fair or poor health and also reported being somewhat or very dissatisfied with life. POEM (p<0.0001) and PO-SCORAD (p<0.0001) were also significantly associated with poor health. Disease severity in all measures was associated to being neither satisfied or dissatisfied, somewhat or very dissatisfied. Adults with moderate and severe AD were less likely to report itch or excessive dryness and scaling as their most burdensome symptoms. A higher proportion reported blisters or bumps, red or inflamed skin, sleep disturbance, pain, and open sores or oozing as their most burdensome symptoms **Lifestyle** Adults with AD reported that AD limited their lifestyle (51.3%), caused them to avoid social interaction because of their appearance (39.1%), and impacted their activities (43.3%). Even patients with mild AD reported that AD limited their lifestyle (34.5%), impacted activities (23.2%), or led to avoidance of social interactions (17.7%) Burden across severity: These harmful effects of AD were even more burdensome in persons with self-reported global moderate and severe AD (p<0.0001 for all). In particular, almost one in two adults with severe AD reported 'quite a bit' or 'a great deal of' burden in these areas
Silverberg J, et al. 2019 A[41]	Cross-sectional	17	Population size: 596 Subgroups: N/A	HRQoL	DLQI	**Association between pain frequency and (adjusted OR [95% CI]):** **PO-SCORAD:** 1.04 (1.01-1.07), p<0.0001 **PO-SCORAD itch:** 1.15 (1.02-1.30), p<0.0001 **PO-SCORAD sleep:** 1.02 (0.92-1.13), n.s. **POEM:** 1.15 (1.02-1.30), p<0.0001

						Association between pain intensity and (adjusted OR [95% CI]): **PO-SCORAD:** 0.06 (0.03-0.08), p<0.0001 **PO-SCORAD itch**: 0.20 (0.08-0.32), p<0.0008 **PO-SCORAD sleep:** 0.07 (-0.01-0.14), n.s. **POEM:** 0.12 (0.07-0.17), p<0.0001 **Association between pain and quality of life (DLQI) (adjusted OR [95% CI])** **PO-SCORAD:** 0.21 (0.17-0.25), p<0.0001 **PO-SCORAD itch:** 0.36 (0.18-0.54), p<0.0001 **PO-SCORAD sleep:** -0.03 (-0.16-0.10), n.s. **POEM:** 0.11 (0.03-0.20), p<0.0001 **Lesions on hands:** 1.32 (0.42-2.22), p<0.004
Silverberg J, et al. 2019 B[42]	Cross-sectional	15	Population size: 2893 Subgroups: 602 AD 2291 non-AD	Emotional health	HADS	**<u>AD vs control</u>** **HADS** Higher proportion of abnormal HADS score (>11) of HADS-A, HADS-D or both (48.4% vs 35.4% vs 26.6%, respectively) AD was associated with significantly higher mean HADS-A and HADS-D, with significantly increased HADS-A and HADS-D scores in patients with moderate and severe/very severe self-reported global AD severity, POEM, PO-SCORAD, PO-SCORAD itch and PO-SCORAD sleep (p<0.0001 for all) Higher self-reported prevalence and diagnoses of anxiety and depression (40.0% AD vs 17.5% non-AD) Higher prevalence of anxiety and depression measured by HADS or reported health-care diagnosis of anxiety or depression (50.3% vs 27.3%)
Silverberg J, et al. 2020[43]	Prospective	18	Population size: 386 Subgroups: 137 mild 123 moderate 116 severe, self-reported by the patient (other classifications if	Cognitive function	PROMIS cognitive function	**<u>Mild vs moderate vs severe</u>** **Patient-reported AD severity (ref: clear) (T-score [95% CI])** Mild: -3.23 (-5.76, -0.71), n.s.; moderate: -5.49 (-8.06, -2.91), p<0.0001; severe: -5.95 (-8.58, -3.32), p<0.0001 **POEM (self-reported) (ref: clear) (T-score [95% CI])** Mild: -1.77 (-2.78, -0.76), n.s.; moderate: -7.62 (-8.75, -6.49), p<0.0001; severe: -5.64 (-6.83, -4.44), p<0.0001; very severe: -18.38 (-20.25, -16.51), p<0.0001 **NRS-Worst Itch (ref: none) (T-score [95% CI])**

			reported by the doctor)			Mild: -0.27 (-1.25, -0.72), p<0.0001; moderate: -3.74 (-4.82, -2.67), p<0.0001; severe: -6.72 (-7.99, -5.45), p<0.0001; very severe: -12.40 (-14.02, -10.77), p<0.0001 **SCORAD-Sleep (ref: none) (T-score [95% CI])** Mild: 0.82 (-0.74, 2.38), n.s.; moderate: -4.00 (-5.77, -2.23), p<0.0001; severe: -6.87 (-8.90, -4.85), p<0.0001 **POEM-Sleep (ref: none) (T-score [95% CI])** 1-2: -0.57 (-1.87, 0.73), n.s.; 3-4: -6.10 (-7.90, -4.31), p<0.0001; 5-6: -3.87 (-5.88, -1.86), p<0.0002; 7: -5.57 (-7.05, -4.09), p<0.0001 **NRS Skin Pain (ref: none) (T-score [95% CI])** Mild: -5.58 (-7.58, -3.58), p<0.0001; moderate: -10.52 (-13.07, -7.97), p<0.0001; severe: -16.81 (-20.07, -13.55), p<0.0001 **SCORAD (Clinically reported) (ref: clear) (T-score [95% CI])** Mild: reference; moderate: -4.08 (-6.86, -1.13), p<0.0001; severe: -11.49 (-14.31, -8.67), p<0.0001 **Cognitive impairment** Significantly higher impairment (assessed with PROMIS-CF related to self-reported AD severity, POEM, EASI, SCORAD, Itch (Worst itch NRS), sleep disturbances (SCORAD-sleep and POEM-sleep) and pain (NRS-Skin pain)
Snyder A, et al. 2021[44]	Cross-sectional	12	Population size: 33 subgroups: 21 patients 12 familiars	HRQoL, sleep disorders, lifestyle and social activities	Ad-hoc questions, self-reported	**HRQoL** Increased frequency and intensity of pain from AD leads to poorer HRQoL **Social isolation** Pain can affect relationships and numerous daily activities. **Sleep impairment** Pain was not always limited to one time of the day and particularly patients and family members experienced negative effects of pain on sleeping
Talamonti M, et al. 2021[45]	Cross-sectional	14	Population size: 352 Subgroups: 174 AD 178 non-AD	Emotional health, HRQoL, sleep disorders	BDI, DLQI, TAS-20, sleep VAS	**<u>AD vs control</u>** **Emotional impairment (mean ± SD)** TAS-20: 52.3 (12.9) vs 45.1 (10.8), p<0.0001 BDI-21: 15.4 (10.2) vs 6.8 (4.8), p<0.0001 **HRQoL (mean ± SD)**

						DLQI** for patients with AD: 13.8 (7.0) ** only AD patients completed DLQI **Sleep disorders** NRS-Pruritus is strongly correlated with sleep disturbance (r=0.5621, p<0.00001) Sleep disturbance is correlated with DLQI score (r=0.2992, p<0.005) and BDI score (r=0.307, p<0.005) **<u>Disease burden according to severity</u>** No statistically significant differences between mild-to-moderate and moderate-to-severe AD patients for emotional health, sleep impairment, pruritus and quality of life
Treudler R, et al. 2020[46]	Cross-sectional	18	Population size: 9481 Subgroups: 372 AD 9109 non-AD	Emotional health, HRQoL, lifestyle and social activities	CES-D, GAD-7, SF-8, LSNS-6	**<u>AD vs control</u>** **Emotional health (OR [95% CI]** CES-D: OR 1.5 (1.0, 2.3), p=0.031 GAD-7: OR 1.5 (1.0, 2.2), p<0.049 **Isolation** LNSN-6 results did not show an association between AD and social isolation **HRQoL (mean)** SF-8 PCS: 46.9 vs 48.0, p<0.001 SF-8 MCS: 50.6 vs 52.5, p<0.001

ABS-A: Atopy Burden Score–Adult; AD: atopic dermatitis; Aderm-IS: Atopic Dermatitis Impact Scale; AIS: Athens Insomnia Score; BDI: Beck Depression Inventory; CES-D: Centre for Epidemiologic Studies Depression Scale; CI: confidence interval; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; EQ-5D: EuroQoL – 5 Dimensions; EQ-5D-3L (EuroQoL – 5 Dimensions 3 Level Version; GAD-7: Generalized Anxiety Disorder – 7; HADS: Hospital Anxiety and Depression Scale; HADS-A: HADS anxiety; HADS-D: HADS-depression; HADS-T: total HADS; HCRU: health-care resource utilization; HR: hazard ratio; HRQoL: Health-Related Quality of Life; IC-AD: inadequately controlled atopic dermatitis; IGA: Investigator Global Assessment; ISI: Insomnia Severity Index; LSNS-6, Lubben Social Network Scale; MCS: mental component summary; mEQ-5D: mapped EQ-5D; N/A: not available; NRS: Numerical Rating Scale; n.s.: not significant; OR: odds ratio; PCS: physical component summary; POEM: Patient Oriented Eczema Measure; PO-SCORAD: Patient Oriented SCORing of AD; PGH: PROMIS Global Health; PGH-M4 T: PGH associated items with mental health; PGH-P4 T: PGH associated items with physical health; PHQ-9: Patient Health Questionnaire; PROMIS-CF: PROMIS Cognitive Function; PROMIS-SD: PROMIS Sleep Disorders; PROMIS-SRI: PROMIS Sleep-Related Impairment; PSQI: Pittsburgh Sleep Quality Index; SA-EASI: Self-Administered EASI; SCORAD: SCORing AD; SD: standard deviation; SF-12: Short Form 12 items; SF-36: Short Form 36 items; SF-6D: Short Form 6-Dimension; SF-8: Short Form 8 items; TAS-20, Toronto Alexithymia Scale – 20; T-score: standardized score; VAS: Visual Analogic Scale; WP: Worst Pruritus; WPAI: Work Productivity and Activity Impairment; #Statistical significance (p-value) not reported