ORIGINAL REPORT

Economic and Humanistic Burden in Paediatric Patients with Atopic Dermatitis

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Data concerning the economic and humanistic burden in patients with paediatric atopic dermatitis (AD) and their families are scarce. This retrospective study investigated these burdens in paediatric patients with AD using maintenance treatment with topical corticosteroids and/or conventional systemic immunosuppressants. Patient-reported outcomes regarding quality of life, AD severity, and parental work-related impairment were completed at inclusion. Data on healthcare resource utilization and medication prescription were collected retrospectively over the previous 12 months. Patients were categorized into mild, moderate or severe AD, based on Eczema Area and Severity Index score and medication use. Costs per patient per year per AD severity category were calculated. A total of 101 patients (median age 11.0 years (interquartile range 7.5–14.0), 47.5% men) were included, of whom 38 had mild AD, 37 moderate AD, and 26 severe AD. Mean ± standard deviation (SD) total costs patient per year for mild, moderate and severe AD were €1,812 ± €1,280, €2,680 ± €3,127, and €5,861 ± €3,993, respectively. Highest total direct and indirect costs were found in patients with severe AD, mainly due to higher healthcare and medication costs. Highest humanistic burden was found in patients with moderate AD. For example, the median (interquartile range) Patient-Oriented Eczema Measure score was significantly higher in these patients compared with mild and severe AD (19.0 (15.0–24.0) vs 12.0 (8.8–15.0) and 17.0 (9.5–22.0), respectively). AD in paediatric patients incurs considerable direct and indirect costs, especially in patients with severe AD. The high humanistic burden in patients with moderate AD underlines the need for effective and safe new treatment options for children with AD.

Key words: atopic dermatitis; economic burden; humanistic burden; health-related quality of life; paediatric.

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SIGNIFICANCE

This study investigated the economic and humanistic burden related to atopic dermatitis severity category in paediatric patients with atopic dermatitis and their families. In 101 paediatric patients with atopic dermatitis, total costs were calculated over the previous 12 months and patient-reported outcomes were completed. Total costs, including direct and indirect costs, increased with the severity of atopic dermatitis. The highest humanistic burden was found in patients with moderate atopic dermatitis, indicating possible undertreatment in this group. These data show that patients with atopic dermatitis incur a considerable impact of humanistic and economic burden. The results emphasize the need for effective and safe new treatment options for children with atopic dermatitis.

Atopic dermatitis (AD) is a chronic inflammatory, itchy skin disease, characterized by exacerbations and remissions. The physician-diagnosed 1-year prevalence of paediatric AD in Europe varies between 1.8% and 17.0% (1, 2). Most patients with paediatric AD have mild AD, which can be well-controlled with intermittent use of low-potency topical corticosteroids and emollients. Approximately 33% of paediatric patients with AD have moderate-to-severe AD, which requires more challenging treatment, including continuous use of more potent topical corticosteroids, systemic immunosuppressants, and/or hospitalization (3).

Due to intensive time-consuming therapy, uncontrollable itch, atopic comorbidities, and difficult-to-control disease, AD has a major impact on the quality of life (QoL) of patients and their families. Humanistic burden, often presented as health-related quality of life (HRQoL) or patient burden, reflects the impact of disease on the QoL of patients, activities of daily living (ADL), caregiver health and caregiver QoL, and is assessed in health economic studies (3–5). Multiple studies have demonstrated that the QoL of paediatric patients and their caregivers reduces as the severity of AD increases (5–7).

Next to the humanistic burden, AD causes an economic burden in terms of direct and indirect costs related to AD (8, 9). Several studies in different countries have shown that the economic burden increases with AD severity (5, 8, 10, 11). A study including 5 countries worldwide showed that costs varied between USD71 (the Netherlands) and USD2.559 (Germany) per patient per year (PPY), depending on the population studied and expenses included

(12). Both the economic and humanistic burden of AD in paediatric patients are often underestimated (13).

Limited data are available on the economic and humanistic burden per AD severity category in paediatric patients with AD and their families. More information on the economic and humanistic burden is needed in order to understand the association between the impact on QoL and costs PPY in paediatric patients with AD. This current study includes patients treated with maintenance treatment with topical corticosteroids and/or conventional systemic immunosuppressants. AD treatment is changing and new systemic therapies are becoming available; this study provides context regarding the value of new treatment options.

The aim of this study was to investigate the economic burden, including direct and indirect costs, and the humanistic burden, including patient-reported outcome measures, in children with mild, moderate, and severe AD and their families in a daily practice setting. Based on previous literature, it is hypothesized that the economic and humanistic burden will increase with severity of AD (14–16).

METHODS

Study design and patient population

This retrospective cohort study included patients with AD from 4 to 17 years old between November 2018 and November 2021. All eligible patients were diagnosed with AD by a dermatologist or paediatrician at least 1 year prior to inclusion (17). All patients were treated at the Department of Dermatology and Allergology of Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU), in the Netherlands. The study was approved by the local medical research ethics committee Utrecht as a non-interventional study (METC 18-725) and was performed according to the Declaration of Helsinki. All patients and/or caregivers gave written informed consent.

Patients were categorized into mild, moderate, and severe AD based on the Eczema Area and Severity Index (EASI) score at inclusion, which was stratified as following: EASI 0–5.9 (mild AD), EASI 6–22 (moderate AD) and EASI 23–72 (severe AD) (18). Patients who were treated with systemic immunosuppressants (cyclosporine A, methotrexate and/or prednisolone) at inclusion or in the previous year were classified as patients with severe AD, regardless of their EASI score at inclusion. Electronic patient files were reviewed by a dermatologist (MdG) to determine severity categories from patients with missing EASI scores and from patients hospitalized for AD in the previous year. Paediatric patients treated with new systemic therapies (e.g. biologics and Janus kinase (JAK)-inhibitors) and patients and parents who were unable to complete Dutch questionnaires were excluded.

Data collection

Depending on the patients' age at inclusion, questionnaires regarding AD, atopic comorbidities, and the economic and humanistic burden of AD were completed by patients and/or their caregivers. Data regarding healthcare resource use were collected retrospectively over a 12-month period. Information about the treatment for AD and atopic comorbidities (asthma, allergic rhinitis, and food allergy) was obtained by analysing electronic medical records from the hospital, pharmacists, the general practitioner (GP), and other healthcare institutions.

Economic burden of disease

Resource utilization. Healthcare resource utilization was categorized into outpatient visits including telephone consultations per healthcare provider and hospitalization. A distinction was made between tertiary and secondary care. Total medication use included systemic immunosuppressants, topical treatment, treatment for atopic comorbidities, and other AD-related treatments (e.g. antibiotics and antihistamines). Furthermore, both self-care products and bandage material/anti-bacterial clothing were taken into account. Diagnostic and laboratory tests were included per patient. Google Maps (Mountain View, CA: Google LLC) was used to determine the geographical distance between the patients' residence and the UMCU. Lastly, absenteeism of employed caregivers was evaluated by the caregivers' reported missed hours of work due to their child's AD.

Costs. The Dutch Costing Manual (DCM) for Economic Evaluations in Health Care, published by the Dutch National Health Care Institute, was used to determine the costs related to AD and atopic comorbidities (19). The DCM describes reference prices from 2014, which were adjusted for inflation until 2021 using the Consumer Price Index constructed by Statistics Netherlands (20). Costs were calculated PPY. All expenses made 1 year prior to inclusion were categorized into direct and indirect costs (Table SI). Direct costs were defined as costs directly related to AD or atopic comorbidities, including healthcare costs (outpatient visits, hospitalization and diagnostic and laboratory tests), medication costs, transportation costs, and estimated out-of-pocket costs. Medication prices (including 9% medication tax) were obtained from the online drugs registry from the Dutch National Health Care Institute (21). Diagnostic and laboratory costs included a laboratory fee, the fee charged for dispensing medication. Indirect costs, defined as costs due to absenteeism of employed caregivers because of their child with AD, were calculated using the human capital method (22).

Humanistic burden of disease

Validated questionnaires were used to examine the patientreported severity of AD, as this could affect QoL, and the impact on QoL of daily and social activities of patients and their families (23–30). These questionnaires were qualified to represent the different dimensions of health (physical and psychosocial), defined as the humanistic burden. The visual analogue scale (VAS), a numerical rating scale from absent (score 0) to severe (score 10), was used to measure pain and itch in the previous 7 days. The Patient-Oriented Eczema Measure (POEM) questionnaire (0–2=clear or almost clear AD, 3–7=mild AD, ≥8=moderate AD, and ≥17=severe AD) was used to evaluate severity of AD during the previous week (23, 24). The EuroQoL 5 Dimensions Youth (EQ-5D-Y) was completed to measure health-related QoL, defined by "problems" or "no problems" (25). The impact of AD on QoL of patients and their families was measured with the Children's Dermatology Life Quality Index (CDLQI) (2–6=small effect, 7–12=moderate effect, and ≥13=large effect) and the Dermatitis Family Impact (DFI) (6–10=low impact, ≥11=moderate impact and >20=high impact). Although anxiety is often reported as a comorbidity in AD, anxiety can additionally affect humanistic burden. Therefore, the paediatric anxiety short-form of the Patient-Reported Outcomes Measurement Information System (PROMIS) was used to report anxiety experienced in the previous 7 days for paediatric patients aged ≥8 years (28, 29). The reported outcomes were rescaled into T-scores using the PROMIS scoring table (T-scores >50 indicated more anxiety compared with the mean population) (31).

Table I. Patient characteristics

	Total cohort (*n*=101)	Mild AD (*n*=38)	Moderate AD (*n*=37)	Severe AD (*n*=26)
Male, *n* (%)	48 (47.5)	19 (50.0)	17 (45.9)	12 (46.2)
Age, years, median (IQR)	11.0 (7.5–14.0)	9.0 (5.0–14.0)	11.0 (9.0–14.0)	14.0 (10.5–15.3)
Age onset AD, years, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.0 (0.0–1.0)
Hospitalized for AD in the previous year, *n* (%)	12 (11.9)	0.0 (0.0)	4 (10.8)	8 (30.8)
Systemic immunosuppressants as treatment for AD in the previous year[a], *n* (%)	26 (25.7)	0.0 (0.0)	0.0 (0.0)	26 (100.0)
Cyclosporine A, *n* (%)	26 (25.7)	0.0 (0.0)	0.0 (0.0)	26 (100.0)
Methotrexate, *n* (%)	3 (3.0)	0.0 (0.0)	0.0 (0.0)	3 (11.5)
Prednisolone, *n* (%)	6 (5.9)	0.0 (0.0)	0.0 (0.0)	6 (23.1)
Mycophenolate mofetil, *n* (%)	1 (1.0)	0.0 (0.0)	0.0 (0.0)	1 (3.8)
Dexamethasone, *n* (%)	1 (1.0)	0.0 (0.0)	0.0 (0.0)	1 (3.8)
Atopic diseases				
Asthma, *n* (%)	42 (41.6)	14 (36.8)	16 (43.2)	12 (46.2)
Allergic rhinitis, *n* (%)	63 (62.4)	21 (55.3)	24 (64.9)	18 (69.2)
Food allergy, *n* (%)	51 (50.5)	19 (50.0)	18 (48.6)	14 (53.8)
EASI, median (IQR)	5.7 (3.0–11.3)	3.1 (1.7–3.9)	11.0 (7.6–15.2)	7.7 (3.4–16.5)
Missing, *n* (%)	9 (8.9)	2 (5.3)	3 (8.1)	4 (15.4)
IGA, median (IQR)	2.0 (2.0–3.0)	2.0 (1.5–2.0)	3.0 (2.0–3.0)	2.0 (2.0–3.2)
Missing, *n* (%)	14 (13.9)	5 (13.2)	4 (10.5)	5 (19.2)

[a]Some patients were treated with multiple systemic immunosuppressants for atopic dermatitis (AD).
IQR: interquartile range; SD: standard deviation; EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment.

Caregivers' work impairment and impairment in daily activities regarding the previous 7 days were measured by using the Work Productivity and Activity Impairment (WPAI) questionnaire for caregivers of AD (30). Higher outcomes of the WPAI indicated greater impairment and less work productivity.

Statistical analysis

Patients were categorized into mild, moderate or severe AD, based on EASI score and/or use of systemic immunosuppressive drugs. The χ^2 test and the Fisher's exact test were used to assess differences between categorical variables. Normally distributed data were expressed as means and standard deviations (SD). Non-normally distributed data were expressed in medians and interquartile ranges (IQR). Costs by AD severity were compared using Kruskal–Wallis H-test. The Pearson's χ^2 test and Mann–Whitney *U* tests were used to compare differences within the severity groups. *p*-values were corrected for multiple testing by use of the Benjamini-Hochberg method, which controls false discovery rate (FDR) (32). For all analyses, a FDR adjusted *p*-value of <0.05 was considered statistically significant. Data analyses were conducted using IBM SPSS Statistics, Version 26 (Armonk, NY: IBM Corp) (33). Figures were created using Prism (GraphPad Prism version 9.3.0 for Windows, GraphPad Software, San Diego, CA, USA).

RESULTS

Patient characteristics

A total of 101 patients (median (IQR) age 11.0 years (7.5–14.0), 47.5% men) were included: 38 with mild AD, 37 with moderate AD, and 26 with severe AD. Median (IQR) age of AD onset was 0 years (0.0–1.0). The highest EASI scores were found in patients with moderate AD (11.0 (IQR 7.6–15.2)) followed by patients with severe AD (7.7 (IQR 3.4–16.5)), and mild AD (3.1 (IQR 1.7–3.9)). Among the total cohort, 11.9% (*n*=12) patients were hospitalized for AD in the previous year and 25.7% (*n*=26) patients were treated with systemic immunosuppressants for AD in the previous year. All other patient characteristics are shown in **Table I**.

Economic burden of disease

Mean total costs, including direct and indirect costs, were €3,145 (SD±€3,265), shown in **Table II** and **Fig. 1**. Mean±SD total costs PPY were €1,812± €1,280

Table II. Total direct and indirect costs per patient per year (mean)

	Total cohort (*n*=101) Mean±SD	Mild AD (*n*=38) Mean±SD	Moderate AD (*n*=37) Mean±SD	Severe AD (*n*=26) Mean±SD	*p*-value*	Adjusted *p*-value
Total direct costs	2,680±2,744	1,512±854	1,984±2,093	5,377±3,518	<0.001	<0.001
Total healthcare costs	1,567±2,129	725±368	1,308±1,859	3,167±3,018	<0.001	<0.001
Total medication costs	709±738	393±394	385±287	1,632±799	<0.001	<0.001
Emollients therapy	110±142	111±151	78±87	156±179	0.113	0.147
Topical corticosteroids	119±117	98±132	105±88	169±118	0.002	0.004
Topical immunomodulators	20±53	21±41	10±22	33±89	0.353	0.382
Systemic immunosuppressants	240±524	0±0	0±0	930±657	<0.001	<0.001
Other medication	74±158	58±134	80±205	91±112	0.004	0.007
Diagnostic (incl. laboratory) costs	63±125	47±85	47±103	108±183	0.002	0.004
Transportation costs	126±112	95±73	114±102	189±147	0.008	0.012
Out-of-pocket costs	215±423	252±548	130±155	281±467	0.853	0.853
Total indirect costs						
Absenteeism caregivers	521±1545	300±847	696±2272	601±929	0.286	0.338
Total costs	3,145±3,265	1,812±1,280	2,680±3,127	5,861±3,993	<0.001	<0.001

AD: atopic dermatitis; SD: standard deviation. All data is presented in Euro (€).
**p*-value <0.05 was considered significant. *p*-values were adjusted for multiple testing using the Benjamini-Hochberg method, controlling the false discovery rate (FDR) (32).

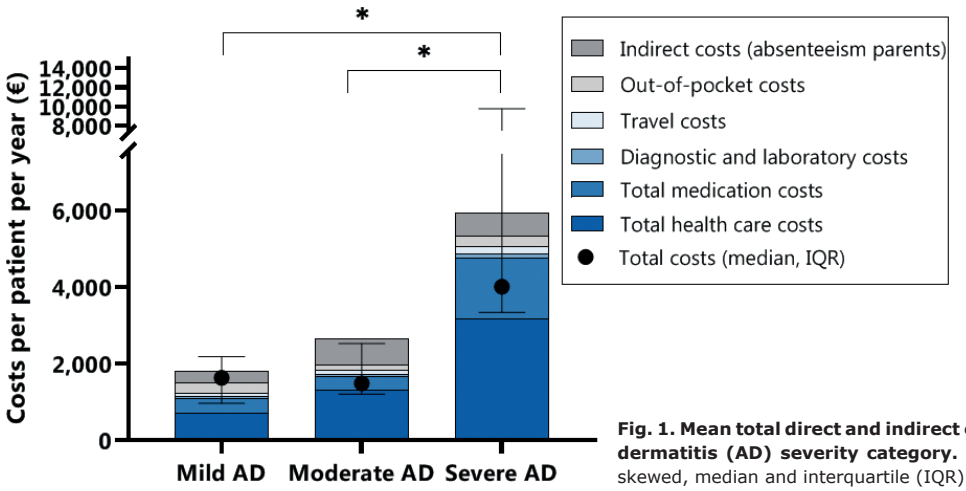

Fig. 1. Mean total direct and indirect costs per cost category and per atopic dermatitis (AD) severity category. Data of costs per patient per year were skewed, median and interquartile (IQR) range are shown.

for mild AD, €2,680±€3,127 for moderate AD, and €5,861±€3,993 for severe AD (p<0.001). Patients with severe AD most frequently visited the outpatient clinic, and were more often hospitalized in the previous 12 months compared with patients with mild or moderate AD. This resulted in significantly higher healthcare utilization costs in patients with severe AD, compared with patients with mild or moderate AD (p<0.001). Indirect costs were highest in patients with moderate AD (€696±2,272), compared with mild (€300±847) and severe AD (€601±929). No significant differences were found within these 3 groups.

Humanistic burden of disease

Among all included patients, the median POEM score was 15.0 (IQR 10.0–20.0) and the median VAS itch was 6.0 (IQR 3.0–8.0) (**Fig. 2, Table III,** Table SII). A significantly higher POEM score was reported in patients with moderate AD, compared with patients with mild AD and severe AD (p<0.001). Subsequently, a higher VAS itch was found in patients with moderate AD compared with patients with mild and severe AD (p=0.003). Median CDLQI scores were comparable within patients with moderate AD and those with severe AD, and were significantly higher compared with patients with mild AD (p=0.003). Since only a few patients were aged 16 or 17 years, limited patients completed the DLQI (n=15) and no statistically significant differences within the severity categories could be analysed. PROMIS T-scores were comparable between all severity groups. School absenteeism, expressed in median days per year, was highest in patients with severe AD (9.0 days (IQR 3.0–20.0)), followed by patients with moderate and mild AD (4.0 days (IQR 1.0–8.8) and 1.0 day (IQR 0.0–3.0), respectively, p=<0.001).

In addition, the median DFI score was slightly higher in families of patients with moderate or severe AD, compared with families of patients with mild AD (p=0.214). Of the employed caregivers, the caregivers of patients with severe AD reported the highest work impairment in days per year (20.0 days (IQR 0.0–60.0), p=0.214).

DISCUSSION

This study investigated the economic and humanistic burden associated with mild, moderate, and severe AD in paediatric patients in the Netherlands. The findings indicate that the total costs increase with AD severity, confirming the study hypothesis. Furthermore, the study found that all severity groups experienced impact on

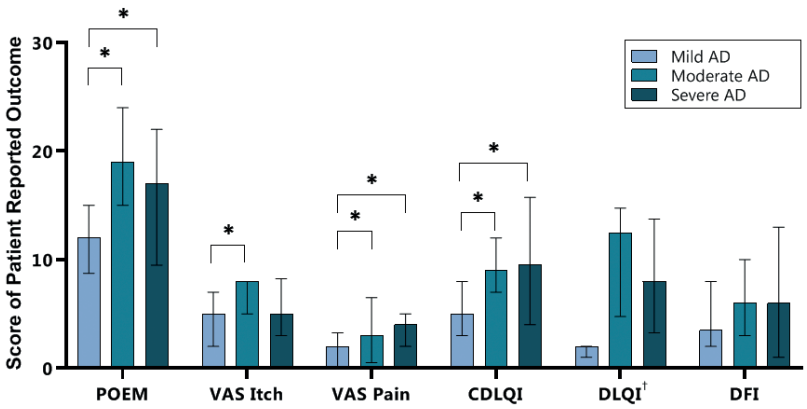

Fig. 2. Results of the patient-reported outcomes. Median and interquartile range (IQR) are shown. Children's Dermatology Life Quality Index (CDLQI) for patients aged 4–15 years (n=86), Dermatology Life Quality Index (DLQI) for patients aged >16 years (n=15). AD: atopic dermatitis; POEM: Patient Oriented Eczema Measure; VAS: Visual Analogue Scale; DFI: Dermatitis Family Impact. †Statistical test was not applicable due to the low number of patients.

Table III. Patient-reported outcomes

	Total cohort (*n*=101)	Mild AD (*n*=38)	Moderate AD (*n*=37)	Severe AD (*n*=26)	*p*-value*	Adjusted *p*-value
POEM, median (IQR)[a]	15.0 (10.0–20.0)	12.0 (8.8–15.0)	19.0 (15.0–24.0)	17.0 (9.5–22.0)	<0.001	<0.001
Missing, *n* (%)	2 (2.0)	0 (0.0)	0 (0.0)	2 (7.7)		
VAS itch, median (IQR)[b]	6.0 (3.0–8.0)	5.0 (2.0–7.0)	8.0 (5.0–8.0)	5.0 (3.0–8.3)	0.001	0.003
VAS pain, median (IQR)[b]	3.0 (1.0–5.0)	2.0 (0.0–3.3)	3.0 (0.5–6.5)	4.0 (2.0–5.0)	0.014	0.037
CDLQI, median (IQR)[b]	8.0 (4.0–12.0)	5.0 (3.0–8.0)	9.0 (7.0–12.0)	9.5 (4.0–15.8)	0.001	0.003
Completed by parents, *n* (%)	86 (85.1)	35 (92.1)	31 (83.8)	20 (76.9)		
DLQI, median (IQR)[c]	6.0 (2.0–13.0)	2.0 (1.0–n/a)	12.5 (4.8–14.8)	8.0 (3.3–13.8)	0.142	0.214
Completed by patients, *n* (%)	15 (14.9)	3 (7.9)	6 (16.2)	6 (23.1)		
DFI, median (IQR)[d]	5.0 (2.3–9.0)	3.5 (2.0–8.0)	6.0 (3.0–10.0)	6.0 (1.0–13.0)	0.110	0.214
Missing, *n* (%)	1 (1.0)	0 (0.0)	0 (0.0)	1 (3.8)		
EQ-5D-Y**, *n* (%)[a]						
Mobility					0.794	0.822
Problems	11 (10.9)	5 (13.2)	3 (8.1)	3 (11.5)		
No Problems	88 (87.1)	33 (86.8)	33 (89.2)	22 (84.6)		
Self-care					0.822	0.822
Problems	27 (26.7)	10 (26.3)	9 (24.3)	8 (30.8)		
No Problems	72 (71.3)	28 (73.7)	27 (73.0)	17 (65.4)		
Daily activity					0.422	0.482
Problems	38 (37.6)	12 (31.6)	14 (37.8)	12 (46.2)		
No Problems	61 (60.4)	26 (68.4)	22 (59.5)	13 (50.0)		
Pain/discomfort					0.147	0.214
Problems	60 (59.4)	19 (50.0)	26 (70.3)	15 (57.7)		
No Problems	39 (38.6)	19 (50.0)	10 (27.0)	10 (38.5)		
Anxiety/depression					0.100	0.214
Problems	42 (41.6)	11 (28.9)	18 (48.6)	13 (50.0)		
No Problems	57 (56.4)	27 (71.1)	18 (48.6)	12 (46.2)		
Missing, *n* (%)	2 (2.0)	0 (0.0)	1 (2.7)	1 (3.8)		
VAS EQ-5D-Y, median (IQR)[a]	80.0 (70.0–90.0)	82.5 (80.0–91.8)	75.0 (70.0–90.0)	65.0 (50.0–79.0)	<0.001	<0.001
Missing, *n* (%)	3 (3.0)	0 (0.0)	1 (2.7)	2 (7.7)		
T-score PROMIS anxiety, median (IQR)[e]	54.8 (50.9–62.1)	53.5 (49.6–58.5)	56.0 (50.9–63.9)	56.0 (49.9–63.0)	0.268	0.357
Missing due to age, *n* (%)	25 (24.8)	13 (34.2)	8 (21.6)	4 (15.4)		
Missing, *n* (%)	4 (4.0)	2 (2.0)	0 (0.0)	2 (7.7)		
Impairment in caregivers' work, median (IQR)[d]	0.0 (0.0–20.0)	0.0 (0.0–17.5)	0.0 (0.0–19.2)	20.0 (0.0–60.0)	0.126	0.214
Missing due to unemployment, *n* (%)	14 (13.9)	5 (13.2)	6 (16.2)	3 (11.5)		
Missing, *n* (%)	10 (9.9)	3 (7.9)	4 (10.8)	3 (11.5)		
Impairment in caregivers' daily activities, median (IQR)[d]	10.0 (0.0–30.0)	10.0 (0.0–22.5)	0.0 (0.0–20.0)	10.0 (0.0–57.5)	0.375	0.462
Missing, *n* (%)	2 (2.0)	0 (0.0)	0 (0.0)	2 (7.7)		
School absenteeism, days per year, median (IQR)[d]	3 (0.1–8.8)	1.0 (0.0–3.0)	4.0 (1.0–8.8)	9.0 (3.0–20.0)	<0.001	<0.001
Missing, *n* (%)	5 (5.0)	1 (2.6)	1 (2.7)	3 (11.5)		

[a]Questionnaire completed by caregivers of patients aged <16 years and by patients aged ≥16 years. [b]Questionnaire completed by caregivers of patients aged <12 years and by patients aged 12–17 years. [c]Questionnaire completed in by patients aged 17 years. [d]Questionnaire completed by caregivers. [e]Questionnaire completed by patients aged ≥8 years.
**p*-value <0.05 was considered significant. *p*-values were adjusted for multiple testing using the Benjamini-Hochberg method, controlling the false discovery rate (FDR) (32).
**EQ-5D-Y, "problems" include "some problems" and "problems" with the concomitant dimension.
IQR: interquartile range; SD: standard deviation; POEM: Patient Oriented Eczema Measure; VAS: visual analogue scale; CDLQI: Children's Dermatology Life Quality Index; DFI: Dermatitis Family Impact; PROMIS: Patient-Reported Outcomes Measurement Information System.

QoL due to AD. The highest impact on QoL was found in patients with moderate AD.

The economic burden of paediatric patients with AD, expressed as the mean±SD total costs PPY, was €3,145±3,265 (equivalent to USD 3,279±3,404, daily exchange rate conversion on 4 July 2022). As disease severity increased, higher expenditures were found in healthcare costs (outpatient visits and hospitalization) followed by medication costs. Patients treated with systemic immunosuppressants were classified as having severe AD, which explains the high medication costs in this group compared with patients with mild or moderate AD. The reported costs are in line with results of studies from Italy (USD 1,540), Germany (USD 2,559), and Singapore (USD 7,943) (8, 10, 12). Consistent with studies from the USA, Italy, Singapore, Australia, and Israel, the costs PPY increased as AD severity increased (5, 8, 10, 11, 34, 35). In line with the current results, a recent study from Israel reported that the highest expenses in paediatric patients with AD were due to frequent healthcare-related visits and higher use of medication (11). Other studies reported different expenses or used different methodology, which complicates the comparison of direct and indirect costs of patients with AD (8, 10, 12). Nevertheless, the trend of these studies is similar to the current study. To compare the economic burden among different countries worldwide, equivalent methodology is necessary, and differences of the various national healthcare systems should be taken into account.

The significant impact on QoL in all severity categories in this paediatric cohort demonstrates the need for improvement in disease management for AD. The highest impact on QoL was seen in patients with moderate AD who also had the highest disease activity, reflected by the highest median EASI score. This implicates that the impact on QoL increases as the disease severity worsens, which is supported by previous studies (5–7). Disease severity and impact on QoL in patients with moderate

AD were higher compared with patients with severe AD. This might be explained by the use of systemic immunosuppressants in patients with severe AD, resulting in better controlled disease with lower humanistic burden. This could indicate that patients with moderate AD in this cohort may have been undertreated and may require systemic immunosuppressants. The decision to initiate systemic immunosuppressants is made on an individual basis and is usually considered in severe cases (36, 37). However, physicians' reluctance to prescribe conventional systemic agents may play a part in this decision, as the side-effect profiles and risks of long-term toxicity are known barriers to prescribing systemic agents, such as cyclosporine A and methotrexate (38). This highlights the unmet need for the development of new, effective, and safe systemic agents for paediatric patients with AD. Recently, new systemic agents have been approved and reimbursed in the Netherlands for the treatment of paediatric patients with moderate-to-severe AD: dupilumab for the treatment of children ≥6 years and upadacitinib for adolescents ≥12 years of age (14–16). These new therapies and the development of future treatment options may address the unmet need in the treatment of children with AD and improve AD disease management.

The high impact on economic and humanistic burden raises the question of what level of costs is acceptable to achieve well-controlled disease, and thus improvement in QoL of paediatric patients with AD. In the current study, patients with severe AD had significantly higher costs compared with patients with mild and moderate AD, and had a lower humanistic burden compared with patients with moderate AD. To establish an association between the level of costs acceptable for controlled disease, a longer follow-up time of these patients is necessary. In particular, when noting the established impact of uncontrolled disease in childhood and in adulthood due to social impact in childhood and/or academic and work-related impact in adulthood, Zuberbier et al. (39) reported that career progression was hindered by AD in 14% of participating adult patients. Ariens et al. (9) showed that work-absenteeism in adulthood leads to high indirect costs, which play an important role in the total costs and could not be taken into account in this paediatric study. Uncontrolled disease is undesirable, and can lead to avoidable socioeconomic costs of AD in terms of lost productivity and effect on learning capacity in younger patients. Furthermore, Zuberbier et al. (39) suggested that both the individual and socioeconomic costs of AD could be reduced if better treatment options were offered, which again indicates the unmet need for safe and effective treatment for AD.

Study limitations

This study has some limitations. The cross-sectional design may have led to recall bias, possibly over- or under-estimating the impact on economic and humanistic burden. However, most data on the economic burden were collected retrospectively using data from healthcare institutions, reducing the risk of bias. Secondly, the COVID-19 pandemic may have influenced the results, as there were fewer physical consultations and more flexibility in the working hours of caregivers, which may have led to an underestimation of costs. Lastly, as this study was conducted in a tertiary expertise AD centre in the Netherlands, the humanistic and economic impact cannot be generalized for patients with AD in primary or secondary care, and may reflect a higher impact on disease burden and costs.

Conlusion

This study shows that AD in paediatric patients incurs a high economic burden, with considerable direct and indirect costs, which increases as the severity of AD increases. In addition, an impact on humanistic burden was found in all patients, especially in the group of patients with moderate AD. Notably, disease activity and impact on humanistic burden was the highest in this group, which may indicate undertreatment of moderate paediatric AD patients, possibly due to a lack of effective and safe systemic agents. This study highlights the unmet need for new and safe systemic agents for paediatric patients with AD. Further research is needed to evaluate the economic and humanistic burden in paediatric patients with AD in relation to the use of new systemic therapies.

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