



# Similarities and Differences in the Perception of Atopic Dermatitis Burden Between Patients, Caregivers, and Independent Physicians (AD-GAP Survey)

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Received: September 28, 2022 / Accepted: October 31, 2022 / Published online: March 15, 2023  
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## ABSTRACT

**Introduction:** Atopic dermatitis (AD)—a chronic inflammatory skin disease characterized by intense itching—can have a detrimental impact on quality of life (QoL). We report results of a quantitative assessment of pediatric patient, caregiver, and physician perceptions of AD burden in children and adolescents.

**Methods:** Pediatric patients (aged 6–11 [children] or 12–17 [adolescents] years) with moderate-to-severe AD, their caregivers, and independent physicians were recruited in 13

countries. Caregivers and their children/adolescents completed an online survey about the impact of AD on 16 key items of patient QoL. Physicians completed surveys on their patients aged 6–11 and 12–17 years. Best–worst scaling was used to rank the importance of the QoL items.

**Results:** Overall, 1447 children/adolescents with moderate-to-severe AD (aged 6–11 years: 701; 12–17 years: 746), 1447 caregivers, and 1092 physicians participated. Patients and caregivers in both age groups ranked disturbed sleep as the most important QoL item, followed by feeling ashamed because of AD. Independent physicians ranked feeling ashamed because of AD as the most important QoL item for both

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s13555-022-00850-7>.

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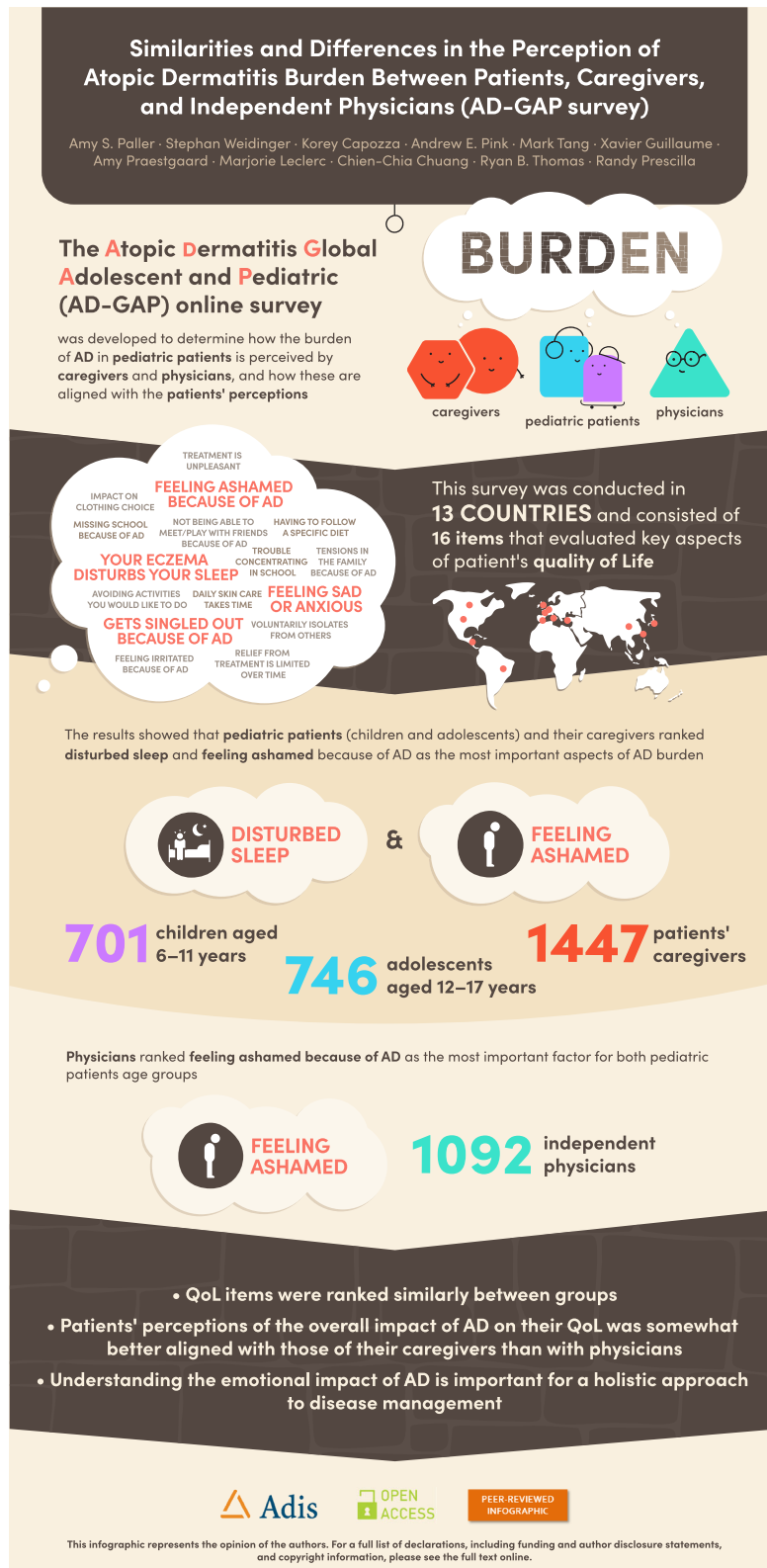
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age groups, followed by disturbed sleep for those aged 6–11 years and being singled out for those aged 12–17 years. The relative importance of the 16 QoL items to patients was strongly aligned between patients in both age groups and their caregivers, but somewhat less so between patients and physicians. Between-country differences were more apparent in physician- versus patient-/caregiver-reported results.

**Conclusion:** The most burdensome QoL items were impact of AD on sleep and feeling

ashamed. Caregivers and physicians correctly identified the QoL items most burdensome to patients. However, patient and caregiver perceptions were generally more closely aligned than patient and physician perceptions. Between-country differences in perceptions (particularly for physicians) were observed, probably due to multifactorial reasons, necessitating further evaluation.

**Infographic:**



**Keywords:** Atopic dermatitis; Quality of life; Best–worst scaling; Dupilumab

### Key Summary Points

#### *Why carry out this study?*

Atopic dermatitis (AD), a chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions, has a substantial negative impact on the quality of life (QoL) of pediatric patients and their caregivers.

Various studies have assessed the impact of AD on the QoL of pediatric patients with AD but, to our knowledge, none have assessed correlations among patient-, caregiver-, and physician-reported impact of disease burden for different QoL aspects among children and adolescents with AD. The purpose of this study was to better understand the perceived burden of AD on child (aged 6–11 years) and adolescent (aged 12–17 years) patients' everyday life and identify discrepancies in patient, caregiver, and physician perceptions of living with moderate-to-severe AD.

#### *What did the study ask? What was the hypothesis of the study?*

The AD Global Adolescent and Pediatric (AD-GAP) survey examined the relative impact of various QoL items for children and adolescents with moderate-to-severe AD as evaluated by the patients themselves, their caregivers, and independent physicians; differences in AD burden perception for children or adolescents between patients, caregivers, and physicians; and differences in AD burden perception for children or adolescents between all participants by country of enrollment.

#### *What were the study outcomes/conclusions?*

Overall, the most burdensome QoL items were the impact of AD on sleep and psychosocial effects on patients aged 6–11 and 12–17 years. Patient, physician, and caregiver perceptions of the most important QoL measures were generally well aligned, and somewhat more so between patients and caregivers than between patients and physicians. There were various between-country differences in perceptions, particularly for physicians.

#### *What has been learned from the study?*

Although physicians and patients generally ranked similar QoL items as the most important, the perception gap between patients and physicians of the relative impact of some aspects of AD on pediatric patient QoL may be more different than has been previously acknowledged.

Appreciating this and understanding the QoL impact of AD in pediatric patients, including the emotional and psychological burden that matters most to each patient, is an important holistic approach to assess AD impact and severity, which can help improve disease management by physicians.

## DIGITAL FEATURES

This article is published with digital features, including a video abstract and infographic, to facilitate understanding of the article. To view digital features for this article, go to: <https://doi.org/10.6084/m9.figshare.22059635>.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions. It is one of the most common chronic diseases, affecting

3–20% of children/adolescents worldwide [1–3]. AD can have a detrimental impact on the quality of life (QoL) of children and adolescents with AD, including factors such as distress due to intense itching, social embarrassment due to visible skin lesions, social isolation, limitations in activities due to skin lesions, fear of triggers, sleep deprivation, and reduced school productivity [4–6]. Caring for children or adolescents with AD can also have a detrimental impact on their caregivers [7–11].

Routine clinical assessments of AD usually focus on evaluation of skin signs, often without capturing the full individual patient burden, including symptoms and QoL impairment. QoL instruments that can collect insights into how pediatric patients (and their caregivers) feel about the impact of AD and of treatments should be more widely used, as studies in other disease areas indicate that there may be discrepancies between the QoL impact felt by the child/adolescent and that perceived by their physician [12–14]. Children's perceptions of their own QoL may change as they mature and may also differ from their parents' perceptions of the impact of AD on their child. To our knowledge, such correlations have not been studied among child and adolescent patients with AD, but some studies in other disease areas have reported good/excellent correlations between child-reported QoL and caregiver-proxy reports (e.g., in patients with acne [15], juvenile fibromyalgia syndrome [16], or epilepsy [17]), while others have reported poor/moderate agreements (e.g., in patients with asthma [18, 19] or impaired mobility [20]). It has also been suggested that caregivers are better at judging physical rather than psychological or emotional aspects of QoL [21, 22]. Hence, the European Academy of Dermatology and Venereology (EADV) recommends QoL measures that include both child/adolescent and caregiver reports [23].

The AD Global Adolescent and Pediatric (AD-GAP) survey, which included children and adolescents with moderate-to-severe AD, was designed to obtain a deeper understanding of pediatric patients' AD burden through patient self-reporting and their caregiver and independent physician perceptions of the day-to-day

AD burden. Following the initial qualitative phase [24, 25], the quantitative part of AD-GAP used standardized questionnaires and ad hoc, semi-structured interviews in 13 countries. Here, we report the results of the quantitative survey, which aimed to: (1) measure the relative importance of various QoL items for child (aged 6–11 years) and adolescent (aged 12–17 years) patients with moderate-to-severe AD as evaluated by the patients themselves, their caregivers, and independent physicians; (2) identify differences in the importance of QoL items on the AD burden perception for children and adolescents among the patients, caregivers, and physicians; and (3) identify differences in AD burden perspectives for children and adolescents between patients, caregivers, and physicians on the basis of country of enrollment.

## METHODS

### Study Design

The AD-GAP survey was a global, cross-sectional, observational survey of children and adolescent patients with moderate-to-severe AD, their caregivers, and independent physicians who regularly manage pediatric patients with AD. It took place between 8 February and 31 March 2021. An appropriately constituted institutional review board (IRB)/ethics committee approved the study (Sterling IRB on 28 January 2021), which was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with applicable regulatory requirements. All patients or/and their parents/guardians and physicians provided written informed consent before participating in the study.

The AD-GAP survey study included two independent parts. An initial qualitative assessment collected self-reported AD burden perceptions from 72 child and adolescent patients with moderate-to-severe AD (aged 6–11 and 12–17 years), and those of their caregivers and independent physicians [24, 25]. The qualitative phase output was used to identify 16 key QoL items most impacted by AD in pediatric patients, which were subsequently used in the

study instrument in the quantitative phase of the survey. In the quantitative assessment, the patient, caregiver, and physician survey instruments allowed for comparison of perceptions/views of AD burden in pediatric patients between the participant groups. Here, we report results of the AD-GAP quantitative assessment.

### Study Population

Caregivers were recruited via general population panels and patients were recruited via their caregivers. Physicians were recruited independently via online panels; hence, recruited physicians were not linked with the recruited caregiver/patient pairs. All participants were recruited using Kantar Profiles panels and national online panels in each country collaborating with them. Panel members were recruited through diverse channels: broad-reach portals, special-interest sites, and direct-email campaigns. Participation was voluntary, and participants could withdraw at any time. Agreement to participate implied consent. All data were pseudonymized to ensure confidentiality and data protection.

Inclusion criteria for the pediatric patients were: (1) patients aged 6–11 or 12–17 years; (2) caregiver-reported diagnosis of AD by a physician and positive responses to the first three International Study of Asthma and Allergies in Childhood (ISAAC) [26] questions completed by the caregivers on behalf of the children or self-completed by adolescents (i.e., itchy rash for  $\geq 6$  months; itchy rash in the past 12 months; itchy rash that at any time affected the skin in the elbow folds, behind the knees, the ankles, under the buttocks, or around the neck, ears, or eyes); (3) clinically active AD, with signs of the disease in the past 12 months (assessed by ISAAC); (4) caregiver/patient self-reported assessment of moderate-to-severe AD (score  $\geq 8$  on Patient-Oriented Eczema Measure [POEM] [27, 28]); and (5) the ability to read and understand the country's native language. Inclusion criteria for the caregivers were: patient's mother or father or any other adult (aged  $\geq 18$  years) caring for the child/adolescent patient with AD, and the ability to read

and understand the country's native language. Inclusion criteria for the physicians were: general practitioners (GPs), dermatologists, pediatricians, or allergists/immunologists in clinical practice for  $\geq 3$  years managing children and adolescents with moderate-to-severe AD, actively treating  $\geq 5$  children/adolescents with moderate-to-severe AD in a typical month, and the ability to read, write, and understand the country's native language.

### Survey Procedures

Recruited participants included pediatric patients, their caregivers, and independent physicians from 13 countries: the USA, Canada, Brazil, Mexico, Italy, Spain, France, the UK, Germany, Turkey, China, Taiwan, and Japan.

An object–case best–worst scaling (BWS) exercise [29] was used to quantitatively assess the perceived relative importance of 16 key QoL items by participants regarding the day-to-day AD burden for children and adolescents. The QoL items were previously identified in the qualitative phase of this study by pediatric patients aged 6–11 and 12–17 years and their caregivers and physicians, validated by a steering committee.

Two separate questionnaires were used (one for the caregiver/patient group and another for the physician group), and both included a BWS exercise. These questionnaires were translated by locally approved translators and administered online in the native language of each country. The QoL survey instrument was completed by children (with caregiver help if needed) and by adolescents (independently of their caregivers).

### Survey Instrument

BWS is a multi-attribute questionnaire that asks participants to select the best and the worst attributes of a specific scenario from a set of three or more attributes in a series of choice tasks/questions. Each attribute is drawn from an attribute set defined by researchers [29, 30].

In the case of this study, participants were asked to select the most and least bothersome items (statements) from a set of four daily-life

**Table 1** Patient, caregiver, and physician characteristics

	Patients ( <i>n</i> = 1447)			Caregivers ( <i>n</i> = 1447)	Physicians ( <i>n</i> = 1092)
	6–11 years ( <i>n</i> = 701)	12–17 years ( <i>n</i> = 746)	Overall ( <i>n</i> = 1447)		
Age in years, mean (SD)	9.3 (1.6)	14.8 (1.6)	12.1 (3.2)	40.1 (7.6)	46.6 (10.3)
Sex, <i>n</i> (%)					
Male	392 (55.9)	445 (59.7)	837 (57.8)	586 (40.5)	N/A
Female	308 (43.9)	301 (40.3)	609 (42.1)	850 (58.7)	N/A
Other	1 (0.1)	0	1 (0.1)	11 (0.8)	N/A
Country, <i>n</i> (%)					
USA	103 (14.7)	98 (13.1)	201 (13.9)	201 (13.9)	150 (13.7)
Canada	29 (4.1)	21 (2.8)	50 (3.5)	50 (3.5)	40 (3.7)
Italy	53 (7.6)	49 (6.6)	102 (7.0)	102 (7.0)	80 (7.3)
Spain	45 (6.4)	55 (7.4)	100 (6.9)	100 (6.9)	81 (7.4)
France	43 (6.1)	57 (7.6)	100 (6.9)	100 (6.9)	80 (7.3)
UK	44 (6.3)	55 (7.4)	99 (6.8)	99 (6.8)	82 (7.5)
Germany	46 (6.6)	50 (6.7)	96 (6.6)	96 (6.6)	80 (7.3)
China	98 (14.0)	101 (13.5)	199 (13.8)	199 (13.8)	150 (13.7)
Taiwan	54 (7.7)	44 (5.9)	98 (6.8)	98 (6.8)	40 (3.7)
Brazil	40 (5.7)	60 (8.0)	100 (6.9)	100 (6.9)	81 (7.4)
Mexico	42 (6.0)	58 (7.8)	100 (6.9)	100 (6.9)	50 (4.6)
Turkey	49 (7.0)	53 (7.1)	102 (7.0)	102 (7.0)	98 (9.0)
Japan	55 (7.8)	45 (6.0)	100 (6.9)	100 (6.9)	80 (7.3)

*N/A* not available, *UK* United Kingdom, *USA* United States

items in a series of 12 questions. Each item was drawn from the 16 QoL-item list obtained during the qualitative phase of the survey. In total, 100 versions of the choice task sets were developed, and these were distributed randomly among respondents. All respondents given the same version had the same choice tasks. This enabled researchers to quantify the relative importance of each of the 16 QoL items for each participant group.

The 16 items related to AD impact on pediatric patients included in the instrument were: (1) trouble concentrating in school; (2) missing

school because of AD; (3) avoiding activities the patient would like to do; (4) eczema disturbing sleep; (5) feeling irritated because of AD; (6) feeling ashamed because of AD; (7) feeling sad or anxious; (8) voluntarily isolating from others; (9) being singled out because of AD; (10) not being able to meet/play with friends because of AD; (11) having family tensions because of AD; (12) daily skin care taking time; (13) treatment being unpleasant; (14) relief from treatment being limited over time; (15) having to follow a specific diet; and (16) impact on clothing choice.



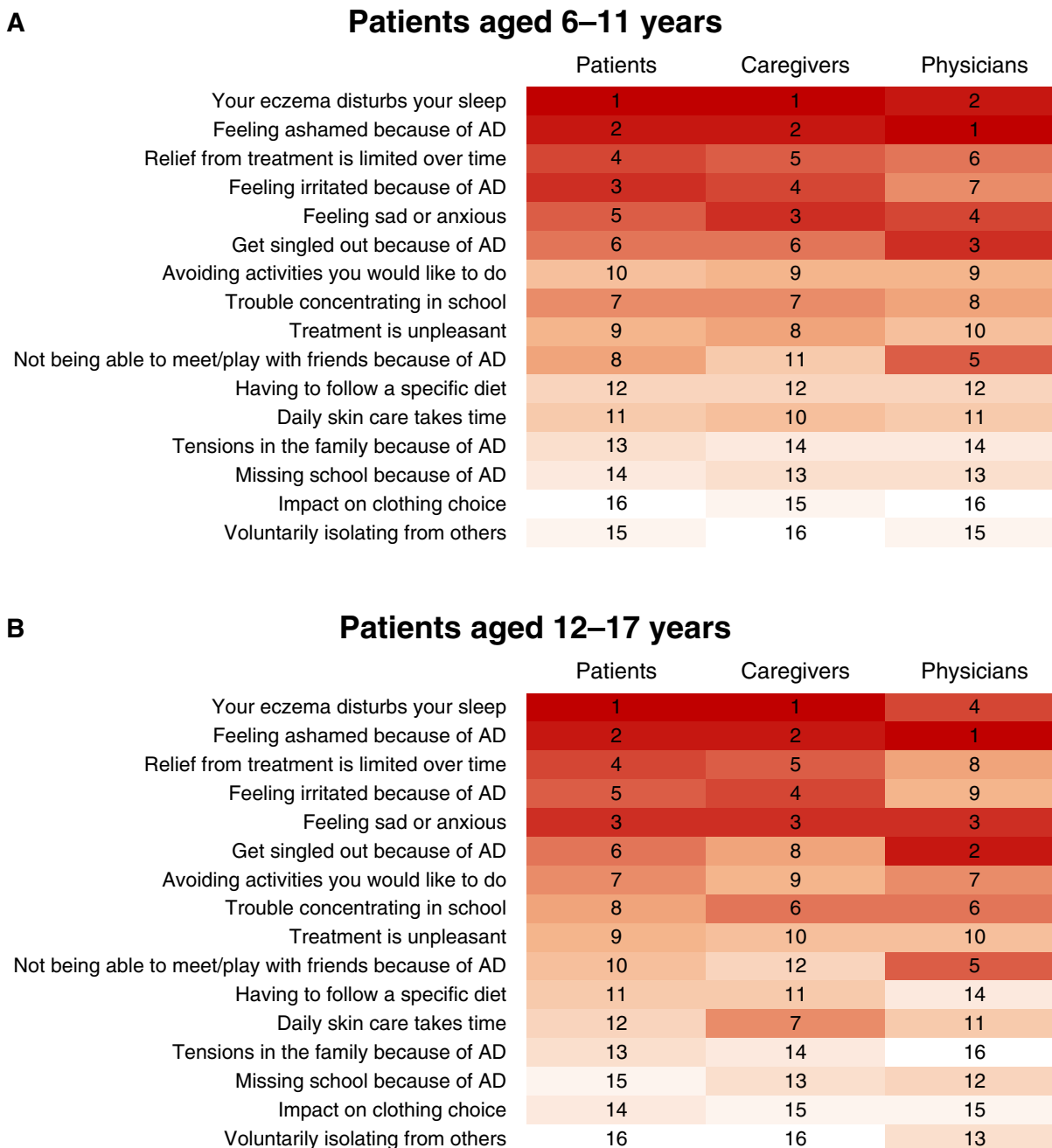
**Table 2** AD severity for pediatric patients aged 6–11 and 12–17 years based on caregiver and POEM<sup>a</sup> assessments

	6–11 years ( <i>n</i> = 701)						12–17 years ( <i>n</i> = 746)					
	By caregiver assessment, <i>n</i> (%)			By POEM, <i>n</i> (%)			By caregiver assessment, <i>n</i> (%)			By POEM, <i>n</i> (%)		
	Moderate	Severe	Very severe	Moderate	Severe	Very severe	Moderate	Severe	Very severe	Moderate	Severe	Very severe
Overall	561 (80.0)	140 (20.0)	18 (2.6)	557 (79.5)	126 (18.0)	18 (2.6)	595 (79.8)	151 (20.2)	16 (2.1)	596 (79.9)	134 (18.0)	16 (2.1)
USA	94 (91.3)	9 (8.7)	7 (6.8)	68 (66.0)	28 (27.2)	7 (6.8)	80 (81.6)	18 (18.4)	5 (5.1)	68 (69.4)	25 (25.5)	5 (5.1)
Canada	24 (82.8)	5 (17.2)	1 (3.4)	24 (82.8)	4 (13.8)	1 (3.4)	17 (81.0)	4 (19.0)	1 (4.8)	13 (61.9)	7 (33.3)	1 (4.8)
Italy	46 (86.8)	7 (13.2)	1 (1.9)	47 (88.7)	5 (9.4)	1 (1.9)	41 (83.7)	8 (16.3)	0	40 (81.6)	9 (18.4)	0
Spain	41 (91.1)	4 (8.9)	0	41 (91.1)	4 (8.9)	0	47 (85.5)	8 (14.5)	2 (3.6)	46 (83.6)	7 (12.7)	2 (3.6)
France	32 (74.4)	11 (25.6)	1 (2.3)	40 (93.0)	2 (4.7)	1 (2.3)	47 (82.5)	10 (17.5)	0	54 (94.7)	3 (5.3)	0
UK	39 (88.6)	5 (11.4)	0	33 (75.0)	11 (25.0)	0	48 (87.3)	7 (12.7)	2 (3.6)	35 (63.6)	18 (32.7)	2 (3.6)
Germany	41 (89.1)	5 (10.9)	2 (4.3)	34 (73.9)	10 (21.7)	2 (4.3)	41 (82.0)	9 (18.0)	2 (4.0)	37 (74.0)	11 (22.0)	2 (4.0)
China	43 (43.9)	55 (56.1)	0	77 (78.6)	21 (21.4)	0	60 (59.4)	41 (40.6)	1 (1.0)	93 (92.1)	7 (6.9)	1 (1.0)
Taiwan	48 (88.9)	6 (11.1)	4 (7.4)	40 (74.1)	10 (18.5)	4 (7.4)	39 (88.6)	5 (11.4)	0	39 (88.6)	5 (11.4)	0
Brazil	26 (65.0)	14 (35.0)	0	33 (82.5)	7 (17.5)	0	53 (88.3)	7 (11.7)	0	49 (81.7)	11 (18.3)	0
Mexico	35 (83.3)	7 (16.7)	0	36 (85.7)	6 (14.3)	0	46 (79.3)	12 (20.7)	0	49 (84.5)	9 (15.5)	0
Turkey	43 (87.8)	6 (12.2)	0	47 (95.9)	2 (4.1)	0	42 (79.2)	11 (20.8)	1 (1.9)	41 (77.4)	11 (20.8)	1 (1.9)
Japan	49 (89.1)	6 (10.9)	2 (3.6)	37 (67.3)	16 (29.1)	2 (3.6)	34 (75.6)	11 (24.4)	2 (4.4)	32 (71.1)	11 (24.4)	2 (4.4)

AD atopic dermatitis, *POEM* Patient-Oriented Eczema Measure, *UK* United Kingdom, *USA* United States

<sup>a</sup>Completed by caregivers for children aged 6–11 years or by the patients themselves for those aged 12–17 years. Scores of 8–16, 17–24, and 25–28 corresponded to moderate, severe, and very severe AD, respectively [27, 28]





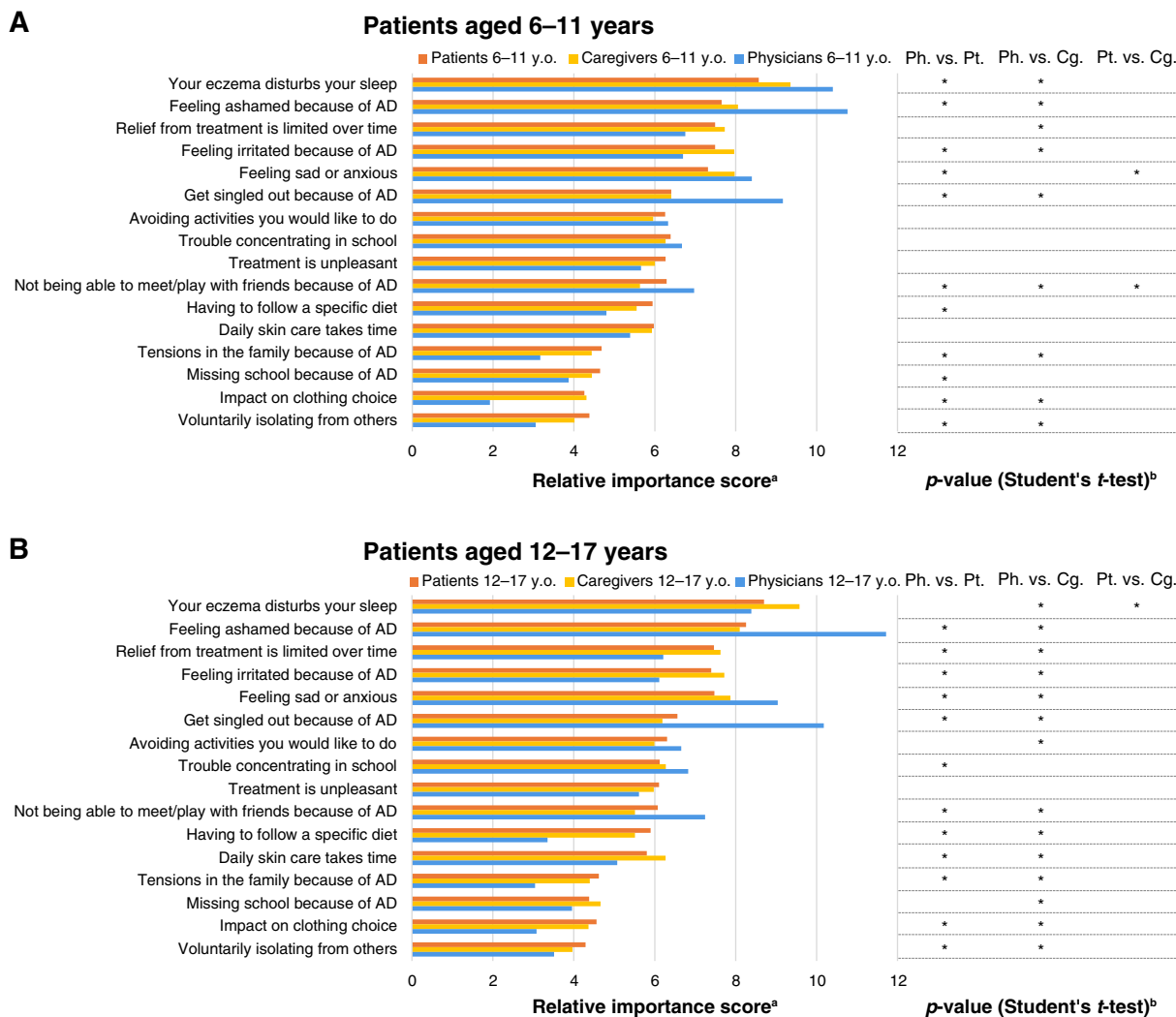
**Fig. 1** QoL item ranking by importance for patients aged **A** 6–11 years and **B** 12–17 years, based on best–worst scores reported by patients, caregivers, and physicians. Colors indicate rank, from most important (dark red) to

least important (white). QoL items are arranged by relative importance reported by patients of both age groups combined. AD atopic dermatitis, QoL quality of life

**Patient/Caregiver Questionnaire**

During screening, caregivers provided information on the average AD severity (mild, moderate, or severe) during the 12 months preceding

the survey of any patient aged 6–11 or 12–17 years in their care. The POEM questionnaire [27, 28] (completed by caregivers of children or the adolescents themselves) was used to



**Fig. 2** Patient-, caregiver-, and physician-reported best-worst scores of QoL items for patients aged **A** 6–11 and **B** 12–17 years. *Cg* caregiver, *Ph* physician, *Pt* patient, *QoL* quality of life, *y.o.* years old. \* $p < 0.001$  (defined significance threshold after multiple-testing correction). <sup>a</sup>RISs were standardized to a total of 100 for each group of participants. A higher RIS indicates a higher importance of an individual item. <sup>b</sup>Traditional parametric *t*-tests were used to determine whether the estimates from the different groups were significantly different from each other. QoL items are arranged by importance scores reported by the overall patient population. No significant differences in

patients' relative importance scoring of QoL item between age groups or according to AD severity based on the defined significance threshold ( $p < 0.001$ ) were found. No significant difference on patient- and caregiver-reported results between the two age groups was found. Physicians' importance scoring for children versus adolescents: disturbed sleep, 10.4 versus 8.4; having to follow a specific diet, 4.8 versus 3.3; impact on clothing choice, 1.9 versus 3.1; feeling ashamed, 10.8 versus 11.7; being singled out, 9.2 versus 10.2; voluntary isolation from others, 3.0 versus 3.5; feeling sad/anxious, 8.4 versus 9.0 ( $p < 0.001$  for all)

define AD activity/severity. Additionally, caregivers were asked how much their child's/adolescent's day-to-day life was affected by AD using a 5-point Likert scale (not at all/a

little/moderately/very/extremely), and patients were asked how much their day-to-day life was affected by AD using the same 5-point scale.

### Physician Questionnaire

As part of the screening, the physicians identified their primary medical specialty, specified their years of clinical practice, the time spent managing pediatric patients with AD, and the split of AD severity (mild, moderate, or severe) in those patients. Physicians also completed two BWS exercises: one for their patients aged 6–11 years with moderate-to-severe AD, and another for their patients aged 12–17 years with moderate-to-severe AD. They were also asked what percentages of their patients aged 6–11 and 12–17 years with moderate-to-severe AD they thought were extremely/very/moderately/a little/not at all affected in their day-to-day life by their disease.

### Statistical Analysis

Target caregiver/patient recruitment was composed of 1450 pairs (200 each from the USA and China; 100 each from Italy, Spain, France, the UK, Germany, Taiwan, Brazil, Mexico, Turkey, and Japan; and 50 from Canada). Target physician recruitment was 1070 (150 each from the USA and China; 80 each from Italy, Spain, France, the UK, Germany, Brazil, Turkey, and Japan; 50 from Mexico; and 40 each from Canada and Taiwan). In each country, a representative sample of the survey population was targeted in terms of patient age groups (aged 6–11 vs. 12–17 years) for the caregiver/patient survey and physician specialties for the physician survey. Epidemiology of Children with Atopic Dermatitis Reporting on their Experience (EPI-CARE) study results were used to estimate representative samples for each country [3].

Participant data (excluding BWS responses) were analyzed descriptively using counts, means, and standard deviations (SDs) for continuous variables and frequencies, and percentages for categorical variables. Country-specific and subgroup analyses were performed to assess associations between subgroups of interest. BWS estimates were calculated using SSI version 8.4.8 (Sawtooth Software, Provo, UT, USA). All remaining analyses were carried out

using DSE version 2.4.8x (DataStax, Santa Clara, CA, USA).

For the BWS exercises [29, 31], mean relative importance scores (RISs) were generated by hierarchical Bayes estimation (Supplementary Material, Text S1), which enabled ranking of perception of disease burden from most to least bothersome. Using this methodology, each of the 16 QoL items identified in the qualitative part of the study were apportioned their share of 100 points, such that the most bothersome items had a larger share and thus a higher score. Traditional parametric *t*-tests were used to determine whether RIS estimates from different groups were significantly different from each other (significance threshold after multiple testing correction was  $p < 0.001$ ). BWS statistical analyses were carried out using SSI Web MaxDiff V8 software (Sawtooth Software, Provo, UT, USA).

## RESULTS

### Participants

Overall, 1447 children and adolescents (701 [48.4%] aged 6–11 years and 746 [51.6%] aged 12–17 years, respectively) participated in the AD-GAP quantitative survey, along with their 1447 caregivers and 1092 independent physicians. There were more male patients (children: 392 [55.9%]; adolescents: 445 [59.7%]) and more female caregivers (850 [58.7%]) (Table 1). The physicians included dermatologists (490 [44.9%]), GPs (283 [25.9%]), pediatricians (207 [19.0%]), and allergists/immunologists (112 [10.3%]). Numbers of participants by country are detailed in Table 1.

By caregiver assessment, most pediatric patients were designated as having moderate AD (children: 561 [80.0%]; adolescents: 595 [79.8%]), with 140 (20.0%) children and 151 (20.2%) adolescents as having severe AD. The proportion of pediatric patients with severe AD varied widely per country, from 8.7% (9, the USA) to 56.1% (55, China) for children, and from 11.4% (5, Taiwan) to 40.6% (41, China) for adolescents (Table 2).

By POEM assessment, most pediatric patients had moderate AD (score 8–16 [27, 28]; children: 557 [79.5%]; adolescents: 596 [79.9%]), with 18.0% of each age group having severe AD (score 17–24 [27, 28]; 126 children; 134 adolescents), and less than 3% of each age group reporting very severe AD (score 25–28 [27, 28]; children: 18 [2.6%]; adolescents: 16 [2.1%]) (Table 2). Per country, the proportion of children affected by severe AD varied from 4.1% (2 patients, Turkey) to 29.1% (16 patients, Japan), and by very severe AD from 0% (Spain, the UK, China, Brazil, Mexico, and Turkey) to 7.4% (4 patients, Taiwan). The proportion of adolescents with severe AD varied from 5.3% (3 patients, France) to 33.3% (7 patients, Canada), and with very severe AD from 0% (Italy, France, Taiwan, Brazil, and Mexico) to 5.1% (5 patients, the USA) (Table 2).

There were large differences in severity levels between caregiver assessment and POEM in some countries but not others (Table 2). In Canada, Italy, Spain, and Mexico, caregiver and POEM assessments for children aged 6–11 years were aligned; in France, China, Brazil, and Turkey, caregiver assessment of disease severity was higher than POEM; and in the USA, the UK, Germany, Japan, and Taiwan, severity was lower by caregiver assessment than POEM. Of note, in the USA and Taiwan, the caregiver assessment of severe disease (USA: 9 children [8.7%]; Taiwan: 6 children [11.1%]) was similar to the very severe AD assessment made by POEM (USA: 7 [6.8%]; Taiwan: 4 [7.4%]).

For adolescents (aged 12–17 years) in Italy, Spain, Taiwan, Mexico, Turkey, and Japan, the caregiver and POEM assessments were aligned; in France and China, adolescents reported less severe disease; and in the USA, Canada, the UK, Germany, and Brazil, the adolescents reported higher disease severity (Table 2).

### Relative Importance of QoL Items

Each QoL item was apportioned its share of 100 points, with a higher RIS indicating the higher importance of an individual item. Patients in both age groups ranked disturbed sleep as the most important QoL item (RIS: children 8.6;

adolescents 8.7), followed by feeling ashamed because of AD (RIS: children 7.6; adolescents 8.3) (Fig. 1; Fig. 2). Feeling irritated because of AD and relief from treatment being limited over time were ranked as the third and fourth most important items for patients aged 6–11 years (RIS: both 7.5 after rounding), followed by feeling sad/anxious (RIS: 7.3) (Fig. 1A; Fig. 2A). For patients aged 12–17 years, feeling sad/anxious and relief from treatment being limited over time ranked third and fourth (RIS: both 7.5 after rounding), followed by feeling irritated because of AD (RIS: 7.4) (Fig. 1B; Fig. 2B). These were also the top five items reported by caregivers, albeit with slight variations in the order of importance (RIS: disturbed sleep, children and adolescents, 9.3 and 9.6, respectively; feeling ashamed, both 8.1; feeling sad/anxious, children and adolescents, 8.0 and 7.9, respectively; feeling irritated, children and adolescents, 8.0 and 7.7, respectively; relief of treatment is limited over time, children and adolescents, 7.7 and 7.6, respectively).

Physicians ranked feeling ashamed because of AD as the most important QoL item for both age groups (RIS: children and adolescents, 10.8 and 11.7, respectively) (Fig. 1; Fig. 2). For patients aged 6–11 years, physician rankings for the remaining top five were disturbed sleep (RIS: 10.4), being singled out (RIS: 9.2), feeling sad/anxious (RIS: 8.4), and not being able to meet/play with friends (RIS: 7.0) (Fig. 1A; Fig. 2A). For patients aged 12–17 years, the items were the same but in a different order of importance (RIS: being singled out, 10.2; feeling sad or anxious, 9.0; disturbed sleep, 8.4; not being able to meet/play with friends, 7.2) (Fig. 1B; Fig. 2B).

### BWS Differences Between Patients, Caregivers, and Physicians

As shown in Fig. 1, patient and caregiver perceptions of the importance of the different QoL items were very similar. Although physicians ranked items in a broadly similar order to patients (Fig. 1), there were some significant differences between physician and patient RISs (Fig. 2).

Compared with patients aged 6–11 years, caregivers assigned significantly higher importance to the impact of feeling sad/anxious (RIS: 8.0 vs. 7.3), and significantly lower importance to the impact of not being able to meet/play with friends (RIS: 5.6 vs. 6.3) (both  $p < 0.001$ ) (Fig. 2). Physicians assigned significantly higher importance to the impact of feeling ashamed (RIS: 10.8 vs. 7.6), being singled out (RIS: 9.2 vs. 6.4), and disturbed sleep (RIS: 10.4 vs. 8.6); along with assigning significantly lower importance to the impact on clothing choice (RIS: 1.9 vs. 4.3), tensions in the family (RIS: 3.2 vs. 4.7), and voluntary isolation (RIS: 3.1 vs. 4.4) (all  $p < 0.001$ ) (Fig. 2).

For patients aged 12–17 years, caregivers only assigned significantly higher importance to the impact of disturbed sleep (RIS: 9.6 vs. 8.7) ( $p < 0.001$ ) (Fig. 2). Physicians assigned significantly higher importance to the impact of being singled out (RIS: 10.2 vs. 6.6), feeling ashamed (RIS: 11.7 vs. 8.3), and feeling sad/anxious (RIS: 9.0 vs. 7.5); along with assigning significantly lower importance to the impact of having to follow a specific diet (RIS: 3.3 vs. 5.9), family tensions (RIS: 3.0 vs. 4.6), and clothing choice (RIS: 3.1 vs. 4.6) (all  $p < 0.001$ ) (Fig. 2).

### BWS Differences Between Age Groups

There were no significant differences between the two age groups in patient- and caregiver-reported results. Physician-reported results were, however, quite different for the two age groups. Physicians scored disturbed sleep (RIS: children vs. adolescents, 10.4 vs. 8.4) and having to follow a specific diet (RIS: 4.8 vs. 3.3) significantly higher for children versus adolescents, but impact on clothing choice (RIS: 1.9 vs. 3.1), feeling ashamed (RIS: 10.8 vs. 11.7), being singled out (RIS: 9.2 vs. 10.2), voluntary isolation from others (RIS: 3.1 vs. 3.5), and feeling sad/anxious (RIS: 8.4 vs. 9.0) were lower for children versus adolescents (all  $p < 0.001$ ).

### BWS Differences Between Countries

Individual QoL item scores for each country by patient, caregiver, and physician for the two age

groups are detailed in Tables S1–S6 (Supplementary Material). These tables also show which scores were significantly higher or lower than those for the overall population. Overall, Taiwan, China, and the USA had the most significantly different scores in comparison to those of the overall population. By participant group, physician-reported results had the most significantly different scores from the overall population, followed by patients, then caregivers.

For patient-reported results among those aged 6–11 years, the most important item was disturbed sleep in Italy, Spain, Germany, China, Mexico, Turkey, and Japan; feeling ashamed in the USA and Canada; feeling irritated in the UK and Brazil; relief from treatment being limited over time in Taiwan; and feeling sad/anxious in France (Supplementary Material, Table S1). For patient-reported results among those aged 12–17 years, the most important item was disturbed sleep in the USA, the UK, Germany, China, Taiwan, Brazil, Turkey, and Japan; feeling ashamed in Canada, Italy, Spain, and France; and being singled out in Mexico (Supplementary Material, Table S2).

For caregiver-reported results among patients aged 6–11 years, sleep was the most important item in all countries except China and Turkey, where it was feeling ashamed, and Japan, where it was feeling irritated (Supplementary Material, Table S3). Sleep was also the most important item for parents of patients aged 12–17 years in all countries except Italy and Germany, where feeling ashamed was ranked most important (Supplementary Material, Table S4).

For physician-reported results among those aged 6–11 years, the most important items varied between countries: disturbed sleep for Spain, Germany, China, Taiwan, and Japan; feeling ashamed for the USA, Canada, Italy, the UK, Brazil, Mexico, and Turkey; and being singled out for France (Supplementary Material, Table S5). For physician-reported results among those aged 12–17 years, feeling ashamed was the most important item in all countries except China, where it was relief from treatment is limited over time, and France, where it was being singled out (Supplementary Material, Table S6).



## Differences in Overall Impact of AD Results Between Patients, Caregivers, and Physicians

Overall, the impact of AD was similar between children and adolescents. Caregivers were more likely than patients to respond that AD moderately affected the patient's day-to-day life (Supplementary Material, Fig. S1). However, while only 1–3% of patients and caregivers reported no effect of AD, physicians reported that 12–14% of their patients were not impacted by AD at all (Supplementary Material, Fig. S1).

### QoL Factors Assessed in Consultations

Physicians were asked how often they specifically ask their patients aged 6–11 and 12–17 years or their caregivers about various QoL measures during consultations to assess patient QoL. While 70% of physicians always/often asked about sleep quality impact, only 35–41% always/often asked about missed school days, with asking about other factors (signs of anxiety/depression and impact on self-esteem, social life, concentration at school, activities and sports, and family life) falling between these extremes (Supplementary Material, Fig. S2).

## DISCUSSION

In the AD-GAP quantitative survey, patients with AD in both the 6–11 and 12–17 age groups ranked disturbed sleep as the most important QoL item, followed by psychosocial factors (such as feeling ashamed, irritated, or sad/anxious) and limited treatment relief over time, the latter stressing the need for more effective and long-lasting treatments for AD. A previous study similarly identified emotional distress and sleep disturbance as the most reported QoL subdomains (after itching/scratching) in pediatric patients with AD aged 0–16 years [32]. Other studies have reported the highest impact of AD to be on school/holidays, itch, and free time/hobbies (for patients aged 5–9 years) or school/holidays, friendships, and either itch or free

time/hobbies (for patients aged 10–16 years) [33, 34].

Caregiver and physician perception of the most important QoL items were generally aligned with that reported by patients, indicating that both caregivers and physicians have a good understanding of what QoL factors most affect patients with AD. Patients aged 6–11 and 12–17 years and their caregivers all ranked disturbed sleep and feeling ashamed because of AD as the two most important QoL items. Physicians ranked feeling ashamed because of AD as most important for both age groups, followed by disturbed sleep for patients aged 6–11 years and being singled out because of AD for patients aged 12–17 years. Physicians ranked disturbed sleep as the fourth most important QoL item in patients aged 12–17 years. This suggests that, as patient age increases, physicians may more heavily weigh the psychosocial factors associated with AD.

There were few significant differences between patient and caregiver responses on the relative impact of various factors on the QoL of children/adolescents with moderate-to-severe AD. We found that the main discrepancies were that caregivers assigned a higher importance to feeling sad or anxious (than patients aged 6–11 years) or disturbed sleep (than patients aged 12–17 years) and assigned a lower importance to not being able to meet/play with friends due to AD (than patients aged 6–11 years). Other than these items, patients and caregivers were well aligned. Combined with literature findings, these results could indicate that patient/caregiver concordance is better for some diseases (such as AD and juvenile fibromyalgia syndrome) than others (asthma) [15, 16, 18, 19], or that concordance varies on the basis of other patient-, caregiver-, or study-related factors. Nonetheless, these results show the benefit of asking pediatric patients directly about their QoL rather than relying on a caregiver report of their child's/adolescent's QoL.

Although physicians recognized the high importance of the impact of AD on sleep and psychosocial issues, there were some significant differences between the relative importance scores of patients and physicians. Most notably, physicians assigned a higher importance to

feeling ashamed, being singled out, and disturbed sleep (patients aged 6–11 years only) and assigned a lower importance to clothing choice, having to follow a specific diet, and family tensions. However, several factors may explain these apparent discrepancies. Firstly, the physicians were not the patients' physicians. Secondly, physicians were answering on the basis of an "average" patient with AD. Thirdly, as patients answered questions on the basis of their own personal circumstances, a range of rankings would have been elicited. All of these likely led to more alignment in the physicians' responses, leading to a wider range of RISs (1.9–11.7 for physicians vs. 4.3–8.7 for patients) and hence higher RISs for physicians versus patients at the top end of the rankings, but lower scores at the bottom end.

As shown in Fig. 1, the rankings of the items were generally quite similar for patients and physicians, with a few notable exceptions (e.g., "not being able to meet/play with friends because of AD" and "get singled out because of AD"), which were given higher importance by physicians than patients, potentially because these are important for affected patients but many are not impacted. Furthermore, different specialties tended to value different dimensions more heavily, with none being very close to the patients' perspective. In both the 6–11- and 12–17-year-old patient groups, dermatologists considered impact on sleep and impact of treatment/skin care as more important. GPs judged psychosocial/living habits dimensions as more important and more frequently perceived their patients as "not at all impacted" than other specialists.

The finding that caregiver/patient responses were better aligned than physician/patient responses could be due to various factors. Firstly, among patients aged 6–11 years, the caregivers are intimately involved in their child's eczema care and could also help their child answer the questionnaire, which could increase concordance, although there was also a high concordance between the adolescents and their caregivers. Secondly, caregivers see and talk with their children much more frequently than physicians do. Lastly, the caregivers and

patients were pairs of respondents, while the physicians were not the patient's physicians.

When asked how often they specifically question their patients (or their caregivers) about various QoL items during QoL consultations, 70% of physicians always/often asked about sleep quality impact, but only 35–40% always/often asked about missed school days, with asking about other factors (signs of anxiety/depression and impact on self-esteem, social life, concentration at school, activities and sports, and family life) falling between these extremes. These results highlight that many psychosocial factors and activities of daily life are not commonly being asked during consultations, which could also help explain why the physicians' expectations of these topics' impact on patients' lives do not necessarily align with patient/caregiver perceptions.

Physicians also underestimated the overall impact of AD on their patients' QoL, with physicians estimating that 12–14% of their patients with moderate-to-severe AD had no QoL impact, compared with only 2–3% of patients indicating no QoL impact. In a previous study, patients reported that physicians sometimes underestimated the physical and emotional impact of AD on their well-being [35]. This is in line with a meta-analysis of nine studies in adults [36] and a more recent study that reported that physicians underestimated the QoL of children/adolescents with inflammatory bowel disease [14]. Overall, these findings stress how important it is that physicians ask individual pediatric patients about different aspects of their QoL in relation to their AD so that they can personalize care and treatment.

As AD often affects pediatric patients, it is important to identify potential differences in the perception of disease impact between patients, their caregivers, and physicians to improve disease management and adherence to therapy. Physicians may tend to focus on the physical aspects of disease rather than the psychological, emotional, and social dimensions and challenges. It is therefore important for physicians to discuss the impact of AD on QoL with patients and base their perceptions on individual patient feedback rather than on their assumptions based on an "average" patient with



AD. Brief, easy-to-use patient-reported outcome tools can be used to make an assessment during consultations, including the Children's Dermatology Life Quality Index (CDLQI) [37] or Skindex-Mini [38, 39] for QoL, POEM [27] for symptoms, and Atopic Dermatitis Control Tool (ADCT) for symptoms and impact of AD on patients' everyday lives and well-being [40]. These assessments should be done periodically, as QoL concerns can change as the child matures. They can also be used to ascertain the effects of treatment, as effective AD therapies such as dupilumab have been shown to improve QoL [41–45].

Differences in perceptions between survey participants across the 13 countries were only observed for some patient- and caregiver-reported BWS compared with the overall population, despite the differences in reported disease severity by country. However, physician-reported BWS was highly variable in the different countries compared with the overall population. China had more severe AD patients in general, and the results for Japan and China were considerably different from those of the overall population. Whether these results could be related to the different proportions of specialists by country (due to healthcare system differences), the AD severity of patients (recruited or by country overall population) or cultural differences is unclear.

### Study Strengths and Limitations

To stratify the previously identified QoL items from the qualitative phase, we used the BWS technique, which has been used in other dermatology studies [30, 46] and is becoming increasingly popular to extract preferences in healthcare [47, 48]. BWS is a common approach for assessing preferences in a healthcare context, being applied in healthcare decision-making, with a strong foundation in psychology and economics. It is a transparent, accessible, and easily comprehensible approach [49], is relatively easy to administer, and may reduce the physical, mental, and time-related burdens a survey can put on patients. The BWS object case data are simple to analyze, adding

confidence to the reported results. The use of the qualitative method in the previous phase to identify the relevant items and provide context also adds confidence to the results of this survey. Lastly, given the geographically broad coverage of subjects participating in the survey, these survey results should be generalizable.

However, there are also some limitations. An online self-reported survey likely underrepresents people without access to, or comfort with, online administration. Furthermore, the self-reported nature of the caregiver/patient survey is associated with potential response biases, such as inaccurate recall, false reporting (whether intentional or unintentional), or biased reporting due to the current health condition of the participant. However, the use of validated instruments (ISAAC and POEM) should limit this bias. Owing to the type of recruitment needed to achieve a high number of respondents, the recruited physicians were not those treating the patients enrolled in the survey. Therefore, one-to-one comparisons were not possible. Children aged 6–11 years could request help of the caregiver if needed to complete the BWS exercise, which could have increased the alignment between the two analyzed groups. However, alignment between adolescents and their caregivers was also high, despite independent completion. Additionally, patients from different countries reported different levels of AD severity, which could have impacted the between-country comparisons, as could the different proportions of specialists by country and the potential for cultural bias.

Finally, the data collected in the BWS exercise were based on responses to hypothetical bothersome AD characteristics. These choices were intended to simulate patient burden as seen from the perspective of the patients themselves, their caregivers, and independent physicians treating patients with AD. Differences could have arisen between stated and actual choices on the basis of the current state of the patient and caregiver, and the specific caseload of each physician at the time the survey was conducted. However, potential bias was limited by the construction of choice questions that mimicked reality as closely as possible [24, 25].

## CONCLUSIONS

The most burdensome QoL items were impact of AD on sleep and psychosocial effects; hence, understanding the emotional impact of AD is important for a holistic approach to disease management. In general, patients, caregivers, and physicians ranked the relative burden of the QoL items similarly. However, the perceptions of pediatric patients aged 6–11 or 12–17 years of the overall impact of AD on their QoL were somewhat better aligned with those of their caregivers than with those of independent physicians. Differences in perception between survey participants across the 13 countries (particularly between physicians) were observed, requiring further evaluation.

## ACKNOWLEDGEMENTS

**Funding.** Research was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. Kantar Health/Cerner Enviza (Paris, France) coordinated the survey data collection and analyzed the results on behalf of Sanofi (Cambridge, MA, USA). The journal Rapid Service Fee was sponsored by Sanofi and Regeneron Pharmaceuticals Inc.

**Medical Writing/Editorial Assistance.** Medical writing/editorial assistance was provided by Maria Coimbra-Dores, PhD, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guideline. The authors thank the patients and investigators who participated in the study, and publication managers Linda Williams and Adriana Mello, who provided support and input.

**Author Contributions.** Amy S. Paller, Stephan Weidinger, Korey Capozza, Xavier Guillaume, Marjorie Leclerc, and Randy Prescilla contributed to study concept and design. Xavier Guillaume and Marjorie Leclerc acquired data and conducted the statistical analyses on the data. All authors interpreted the data, provided

critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

**Prior Presentations.** Weidinger S, Capozza K, Pink AE, Tang M, Prescilla R, Paller AS. AD-GAP: a global, cross-sectional, qualitative survey of children/adolescents aged 6–17 years with moderate-to-severe atopic dermatitis, and their caregivers and physicians. Poster presented at the 20th Annual Meeting of the European Society for Pediatric Dermatology (ESPD 2021); Virtual Meeting; 12–14 May 2021a. Weidinger S, Capozza K, Pink AE, et al. Results from the AD-GAP survey—a qualitative analysis of patient/caregiver/physician perceptions on the impact of moderate-to-severe atopic dermatitis in children and adolescents. Poster presented at the 46th Annual Meeting of the Society for Pediatric Dermatology (SPD) 2021; Virtual Meeting; 8–10 July 2021b. Weidinger S, Capozza K, Pink AE, et al. Relative importance of distinct aspects of quality of life for patients aged 6–11 and 12–17 years with atopic dermatitis, caregivers, and physicians (AD-GAP). Poster presented at the 30th Congress of the European Academy of Dermatology and Venereology (EADV 2021); Virtual Meeting; 29 September–2 October 2021c.

**Disclosures.** Amy S. Paller has been an investigator for AbbVie, AnaptysBio, Dermavant, Eli Lilly, Incyte, Janssen, Krystal Biotech, Regeneron Pharmaceuticals Inc., and UCB; a consultant for AbbVie, Abeona Therapeutics, Alcimed, Almirall, Amagma, AnaptysBio, Arena Pharmaceuticals, Azitra, BiomX, Boehringer Ingelheim, Castle Creek Biosciences, Catawba Research, Eli Lilly, Excicure, Forté, Kamari Pharma, LEO Pharma, LifeMax, NAOS, Novartis, Pfizer, Phoenix, Pierre Fabre, Regeneron Pharmaceuticals Inc., Sanofi, Seanergy, Trifecta Pharmaceuticals, and UCB; and on the data safety monitoring board for AbbVie, Bausch Health, Galderma, InMed Pharmaceuticals, and Novan. Stephan Weidinger is an investigator in the Treatment of Atopic Eczema (TREAT) Registry Taskforce Germany; has received research grants from LEO Pharma, L'Oréal, Novartis, and

Pfizer; been a consultant for Incyte, LEO Pharma, Novartis, Regeneron Pharmaceuticals Inc., and Sanofi; and received speaker fees from AbbVie, Galderma, LEO Pharma, Regeneron Pharmaceuticals Inc., and Sanofi. Korey Capozza is a consultant for Incyte and Sanofi. Andrew E. Pink is a consultant and speaker for Almirall, Eli Lilly, La Roche-Posay, LEO Pharma, Novartis, and Sanofi. Mark Tang has received speaker fees and is an advisory board member for Bioderma, Galderma, GSK, Hyphens Pharma, Kao, LEO Pharma, Menarini, Regeneron Pharmaceuticals Inc., and Sanofi. Xavier Guillaume has no conflicts of interest to disclose. Ryan B. Thomas is an employee and shareholder of Regeneron Pharmaceuticals Inc. Marjorie Leclerc has no conflicts of interest to disclose. Amy Praestgaard, Chien-Chia Chuang, and Randy Prescilla are employees of Sanofi and may hold stock and/or stock options in the company.

**Compliance with Ethics Guidelines.** The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. The local institutional review board or ethics committee at each study center oversaw study conduct and documentation. All patients, or/and their parents/guardians, and physicians provided written informed consent before participating in the study. Pediatric patients provided assent according to the Ethics Committee (Institutional Review Board [IRB]/Independent Ethics Committee)-approved standard practice for pediatric patients at each participating center.

**Data Availability.** Qualified researchers may request access to study documents (including the study report, study protocol with any amendments, statistical analysis plan) that support the methods and findings reported in this manuscript.

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