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ORIGINAL RESEARCH

Multidimensional Burden of Moderate-to-Severe Atopic Dermatitis in Adolescent and Adult Patients from Portugal and Greece: Results from the Global Cross-Sectional Study MEASURE-AD

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ABSTRACT

Introduction: Despite significant progress observed in the treatment of atopic dermatitis (AD), a considerable number of patients with severe disease are undertreated and have inadequate symptom control. This may be due to several reasons, such as underestimation of the implications of the disease on patients, families, and society, as well as inconsistent access to effective treatment. The multidimensional disease burden of AD includes other atopic comorbidities, sleep disturbance, and functional impairment and secondary consequences, including neuropsychiatric issues (anxiety and depression) and reduced health-related quality of life.

Methods: MEASURE-AD was a global, cross-sectional observational study in adolescents and adults with moderate-to-severe AD, conducted to describe disease burden, treatment patterns, and healthcare resource utilization.

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Results: The results concerning patients from Portugal and Greece indicate moderate-to-severe disease for most of the population with frequent disease flares. The quality of life of both adolescents and adults was greatly affected, mainly owing to itch. One out of five patients perceived that their treatment was not effectively controlling AD. Disease resulted in important out-of-pocket expenses and loss of productivity.
Conclusions: Understanding and recognizing the complex burden of moderate-to-severe AD is required to encourage and guide changes in public policy for the effective management of patients.

Keywords: Atopic dermatitis; Burden of disease; Expenses; Productivity; Quality of life; Symptom control

Key Summary Points

Why carry out this study?
A considerable number of patients with severe atopic dermatitis are undertreated and have inadequate symptom control. The burden of atopic dermatitis includes itch, several comorbidities, sleep disturbance, functional impairment, and reduced health-related quality of life accompanied by increased out-of-pocket expenses.
To better understand the existing gaps, a cross-sectional observational study in adolescents and adults with moderate-to-severe atopic dermatitis was conducted to describe disease burden, treatment patterns, and healthcare resource utilization.
What was learned from the study?
Results from Portugal and Greece indicate moderate-to-severe disease for most of the population with frequent disease flares. The quality of life was greatly affected, mainly owing to itching, while 20% patients perceived that their treatment was not effectively controlling the disease. Important out-of-pocket expenses and loss of productivity were noted.
Understanding and recognizing the complex burden of moderate-to-severe atopic dermatitis (AD) is required to encourage and guide changes in public policy for the effective management of patients with AD.

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INTRODUCTION

Atopic dermatitis (AD) is a common chronic, systemic, inflammatory disease that manifests as highly pruritic and painful skin lesions with a significant physical, psychological, and economic burden. This burden increases with disease severity and includes persistent itch, skin pain, sleep and mental health disturbances, and reduced quality of life.

The reported severity of AD varies depending on the countries and the scale used. Milder disease is observed among countries that have an overall continental climate relative to a greater prevalence of individuals with moderate and severe disease in countries with a more northerly or diverse range of latitudes and climate [1–3]. Moderate-to-severe disease is reported in 20% of patients in Europe overall [4], while in southern European countries patients with AD have 49–56% and 10–13% moderate and severe disease, respectively [3]. In all cases, very little is known about the impact, treatment, and use of healthcare resources in this subset of patients with moderate-to-severe disease [1, 2].

The pathophysiology of AD is driven by genetics, environmental factors, and immune dysfunction, leading to chronic inflammation and epidermal barrier defects. This is a highly complex process and involves multiple

cytokines, immune cells, and inflammatory mediators. Atopic dermatitis most often begins in early childhood and has a variable disease course with symptoms persisting into adulthood for many patients [5, 6]. It is currently recognized as a heterogeneous chronic disease with intermittent periods of disease activity—flares—throughout the life of the patient [7]. The recent European guidelines on AD define AD severity using the Scoring Atopic Dermatitis (SCORAD) score or clinically by the severity of the eczema. SCORAD < 25 or transient eczema is considered mild, SCORAD 25–50 or intermittent eczema is considered moderate, and SCORAD > 50 or persistent eczema is considered severe. For moderate disease, proactive therapy with topical calcineurin inhibitors (TCI) or topical corticosteroids (TCS), wet wrap therapy, ultraviolet (UV) therapy, psychosomatic counseling, and climate therapy is recommended. Systemic treatment, including biologics, is recommended only for patients with a high composite score, such as a SCORAD above 50 (scale definition), for patients clinically failing to respond to an appropriately conducted topical therapy (functional definition), or for patients unable to participate in normal daily life activities while following an adequate treatment regimen [8]. The decision for systemic treatment should follow an individualized approach per patient. A signs-only score, such as the Eczema Area and Severity Index (EASI), is not always an adequate tool to decide whether to provide or decline systemic therapy to an individual patient [8]. Therefore, treatment patterns provide another approximation to define AD severity in a real-world setting.

Despite recent advances in effective treatments, a considerable number of patients with severe forms of the disease are undertreated and have inadequate control of their symptoms [4]. This undertreatment may be owing to several reasons, such as underestimation of the full economic, social, and humanistic implications of AD on patients, families, and society, as well as inconsistent access to effective treatment and standards of care. Recognizing the complex burden of moderate-to-severe AD is required to encourage a much-needed change in public policy for the recognition, treatment, and care of patients with the disease [4].

Substantial gaps in our understanding of the impact of AD on the lives of adolescents and adults remain, especially those with moderate-to-severe forms of the disease [9–11]. Recent studies in patients with moderate-to-severe AD disease reported the presence of a multidimensional disease burden that includes other atopic comorbidities (asthma, food allergies, allergic rhinitis, etc.), daily effects associated with pruritus such as sleep disturbance and functional impairment with decreased productivity, and secondary consequences, including neuropsychiatric issues (anxiety and depression) and reduced health-related quality of life [1, 12–14]. In addition, AD causes important out-of-pocket expenses related to the treatment of the disease [15–17].

Adults tend to have more persistent, chronic AD with atypical presentations and higher systemic comorbidities, while adolescents experience more allergic comorbidities and psychosocial burdens. The impact on quality of life is substantial in both groups but manifests differently in terms of social, educational, and occupational challenges [1, 18–21].

To address these gaps, MEASURE-AD, a global cross-sectional study in adolescents and adults with moderate-to-severe AD, was conducted to describe patient burden, treatment patterns, and healthcare resource utilization (HCRU) in dermatological clinics and offices, in multiple domains, in a large well-characterized sample across multiple geographies [22]. The present publication concerns the cluster of patients in Portugal and Greece, two countries with paucity in published data. The available data for the two countries are summarized below.

The published data on the epidemiology of AD in the Portuguese population shows that approximately 0.7–1.6% of the Portuguese adult population was seen in 2017 by a dermatologist for AD, out of which 40–45% had moderate or severe disease. An increase in the number of patients has been reported by physicians over the last years. Most of the newly diagnosed patients are of young age and in the pediatric population, and 14.4% of children under 16 years of age attending dermatology consultation have AD [23]. Similarly, Carvalho

et al. reported a prevalence of atopic eczema in Portugal around 0.61–2.64% [24].

In Greece, there are limited available data on AD prevalence in the adult population, with the results of a recently conducted nationwide survey indicating a range between 2% and 6%, depending on the AD definition used [25]. Similar results were reported in an analysis deriving from the same study, with the 12-month and lifetime self-reported prevalence of AD in adults in Greece ranging from 1.7 to 6.4% and 3.7 to 11.4%, respectively, while at least half of the adults with AD reported moderate-to-severe disease [25].

With the current study, we aimed to describe the burden of disease in adolescent and adult patients with moderate-to-severe AD, the treatment patterns, and healthcare resource utilization in Portugal and Greece. The reason that these two countries were clustered is that they are quite similar in terms of size, population, socioeconomic parameters, climatic conditions, and diet, and in this manner, the sample size could be substantially increased. A similar approach has been implemented by other countries, such as Austria and Switzerland [26]. The findings of the study will provide a better understanding of the burden of disease and facilitate the shaping of policies for an improved treatment of patients with AD.

METHODS

MEASURE-AD was a multicountry, multicenter, cross-sectional observational study. The primary objective of the study was to characterize the multidimensional burden of disease in adolescents and adults with moderate-to-severe AD. The results of the present publication concern the patients included in Portugal and Greece.

This study has received approval from the institutional review boards of all involved institutions. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects (or that person's parent or legal guardian) provided informed consent to participate in the study. The patients included were ≥ 12 years of age with a confirmed diagnosis of moderate-to-severe AD who were candidates or were receiving systemic therapy for AD and had medication history available within the last 6 months. The enrollment of patients occurred in dermatology clinics (universities and hospitals) and offices. All required ethical approvals were obtained by the relevant committees.

Demographic data collected included age, sex, body mass index (BMI), family history of atopic disease, education, marital status, family income, time of diagnosis, time of onset of the disease, type 2 (T helper 2)-driven comorbidities (asthma, allergies, and rhinitis), and selected comorbidities (diabetes, anxiety disorder, depression, high blood pressure, heart disease, autoimmune disease, and obesity (BMI ≥ 30).

The primary endpoints of the study were the Pruritus Numerical Rating Scale assessing worst itch within the past 24 h and the Dermatology Life Quality Index (DLQI), while the secondary endpoints consisted of several measurements of both physician- and patient-reported disease burden.

The evaluation of the patients was carried out using the following tools and questionnaires:

- Physician-reported disease severity and therapies:
    - Scoring Atopic Dermatitis (SCORAD) scale [27].
    - The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD).
    - The Eczema Area and Severity Index (EASI) [28–30].
    - Body surface area (BSA) of AD.
    - Current AD therapy (medications within the past 7 days).
    - Patient-reported disease severity: Patient Oriented Eczema Measurement (POEM) score [14, 28].
- Patient-reported disease control:
    - Inadequately controlled atopic dermatitis.
    - Atopic Dermatitis Flare Questionnaire [31].

- Patient-reported itch:
  - Worst Pruritus Numerical Rating Scale.
  - 5D-Pruritus Scale assessing itch duration [32].
- Patient-reported sleep: Atopic Dermatitis Impact Scale sleep domain (ADerm-IS).
- Patient-reported skin pain: Atopic Dermatitis Symptom Scale (ADerm-SS).
- Patient-reported mental health: Hospital Anxiety and Depression Scale (HADS-A and HADS-D) [33].
- Patient-reported health-related quality of life: The 12-Item Short Form Health Survey (SF-12) and the SF-10 Health Survey for Children (SF-10) [34, 35].
- Dermatology Life Quality Index (DLQI) [36, 37].
- Patient-reported healthcare resource utilization (HCRU):
- Number of healthcare visits in the last 6 months due to AD.
- Number of acute care visits in the last 6 months due to AD.
- Work Productivity and Activity Impairment Index: Atopic Dermatitis (WPAI:AD) [38].
- Out-of-pocket expenses.

Descriptive analysis was performed by variable for patients with available information (e.g., valid percentages). No imputation of missing values was performed. Statistical significance was assessed using a Kruskal–Wallis test for quantitative variables and a chi-squared test for qualitative variables. All analyses were based on observed data.

RESULTS

Demographics

In total, 139 patients, 59 from Portugal and 80 from Greece, were included in the study. Demographic data of the patient population are presented in Tables 1 and 2. The majority of the population were adults (87%), equally distributed among males and females. The mean body mass index (BMI) was 24.35 standard deviation (SD) ± 4.49 kg/m^2, while 47.1% of the patients were overweight/obese. Compared with the population of all subjects enrolled in the global MEASURE-AD study, there were no major discrepancies in what concerns the mean (±SD) age (37.2 ± 16.9 years) and the mean BMI (25.3 ± 5.0 kg/m^2) [22].

Disease Characteristics and Clinical Burden

The mean age of the disease onset for the entire study population was 12.6 ± 15.11 years, while for the adults and the adolescents it was 13.6 ± 15.8 and 5.6 ± 5.0 years, respectively. The mean time from disease onset to diagnosis for all patients was 1142.2 ± 2962.6 days and for the adults and adolescents it was 1269 ± 3152.9 and 296.8 ± 525.9 days, respectively.

In addition, 59 patients (42.4%) reported AD family history, while 76.3% and 33.1% of the patients reported an atopic and a non-atopic comorbidity, respectively (Tables 3 and 4).

The clinical burden of the disease was evaluated with the tools described in Methods.

The mean SCORAD score was 39.8 ± 20.5, and 71.7% of patients had a score ≥ 25.0, indicating moderate-to-severe disease for the majority of the population at the time of the visit.

The mean vIGA-AD score was 2.45 ± 1.121 for the entire population (adults: 2.40 ± 1.144; adolescents: 2.76 ± 0. 903), indicating mild-to-moderate disease, while 54.3% of patients had a vIGA-AD score ≥ 3.0. The same level of severity was also recorded using the EASI score, with 38.8% of patients with mild (EASI = 0.1–5.9) and 39.6% of patients with moderate disease (EASI = 6.0–22.9). Overall, 33.3% of patients had an EASI score ≥ 16.0.

The mean BSA of AD was 19.8 ± 19.2%, and 60.4% of patients presented a BSA ≥ 10.0%.

In terms of symptoms, pruritus was reported by 127/139 patients with a worst pruritus on a numerical rating scale (NRS) mean score of 5.1 ± 2.9. The pruritus NRS score for 65.4% of patients was ≥ 4.0, indicative of moderate-to-severe disease [39]. The duration of pruritus,

Table 1 Demographics of patients from Portugal and Greece included in the study: age, height, weight, body mass index, annual family income

Variable	Age group	N_{Valid}	Mean (SD)	Min	Med	Max
Age [years]	Adolescents	18	13.8 (1.5)	12	13.0	17
	Adults	121	36.3 (14.2)	18	31.0	74
	Total	139	33.4 (15.2)	12	30.0	74
Height [cm]	Adolescents	18	159.7 (9.3)	148	160.5	175
	Adults	121	170.1 (9.3)	151	170.0	197
	Total	139	168.7 (9.9)	148	169.0	197
Weight [kg]	Adolescents	18	54.0 (10.8)	36.1	53.50	80.0
	Adults	121	72.2 (15.9)	35.1	70.00	117.6
	Total	139	69.8 (16.5)	35.1	68.00	117.6
BMI [kg/m^2]	Adolescents	18	21.04 (2.82)	15.4	21.44	26.1
	Adults	121	24.84 (4.49)	15.4	24.38	41.1
	Total	139	24.35 (4.49)	15.4	23.53	41.1
Yearly family income [USD]	Adolescents	14	$32,317.6 ($20,583.77)	$28	$29,645.0	$78,650
	Adults	108	$811,883.7 ($8,147,610)	$0	$24,200.0	$84,700,000
	Total	122	$722,425.3 ($7,665,839)	$0	$24,200.0	$84,700,000

BMI body mass index, *min* minimum, *med* median, *max* maximum, *USD* United States Dollar

recorded in the 5-D Pruritus Scale, was ≥ 6 h/day as reported by 54.0% of the patients.

Disease flares were frequent despite treatment; in the 6 months prior to enrollment, 31.5% of patients had at least five flares with a mean duration of 14.2 ± 21.3 days.

For all the above scores and measurements, no statistically significant differences were observed between the adult and adolescent patients, although, in all cases, adolescents presented numerically higher scores than the adults.

Quality of Life

The quality of life of both adolescents and adults was affected to an important extent, with 73.3% of the adolescents (age < 16 years) and 72.7% of patients aged ≥ 16 years reporting a DLQI score ≥ 6.0. From the single items of the index, in both age groups, "itchy, sore, painful, stinging skin" and "embarrassed/self-conscious" were the two items that had the highest ratings as impacting "a lot/very much" the patients' lives.

Anxiety and depression were evaluated with the HADS-A and HADS-D scores: in 32.5% and 23.8% of patients, a borderline abnormal (≥ 8) HADS-A and HADS-D score was observed, respectively. The mean HADS-A and HADS-D scores were 6.2 ± 3.84 and 5.1 ± 3.54, respectively.

The quality of sleep was affected since patients reported 2.9 nights in which sleep was disturbed over the past week, and 21.6% of the patients reported that their sleep problems interfered much or very much with their daily function over the past week.

About 28% of the patients had combined endpoints with EASI indicating at least moderate severity of AD (Table 5).

On the basis of POEM, 40.9% of patients reported severe AD (POEM score 17–28), and the mean score of the study population was

Table 2 Demographics of patients from Portugal and Greece included in the study: gender, body mass index in categories, highest level of education, marital status, annual family income in categories

	Age group		
	Adolescents *n* (%)	**Adults *n* (%)**	**Total *n* (%)**
Gender			
Male	11 (61.1)	59 (48.8)	70 (50.4)
Female	7 (38.9)	62 (51.2)	69 (49.6)
Total	18 (100.0)	121 (100.0)	139 (100.0)
BMI (grouped)			
Underweight	1 (5.6)	8 (6.6)	9 (6.5)
Normal	16 (88.9)	56 (46.3)	72 (51.8)
Overweight	1 (5.6)	42 (34.7)	43 (30.9)
Obese	0 (0.0)	15 (12.4)	15 (10.8)
Total	18 (100.0)	121 (100.0)	139 (100.0)
Highest level of education			
No formal education	0 (0.0)	2 (1.7)	2 (1.4)
Primary school	4 (22.2)	2 (1.7)	6 (4.3)
Secondary school and/or professional schooling	13 (72.2)	43 (35.5)	56 (40.3)
University	1 (5.6)	52 (43.0)	53 (38.1)
Higher education	0 (0.0)	22 (18.2)	22 (15.8)
Total	18 (100.0)	121 (100.0)	139 (100.0)
Marital status			
Single	15 (83.3)	72 (59.5)	87 (62.6)
Married/civil union	3 (16.7)	40 (33.1)	43 (30.9)
Separated	0 (0.0)	1 (0.8)	1 (0.7)
Divorced	0 (0.0)	7 (5.8)	7 (5.0)
Widowed	0 (0.0)	1 (0.8)	1 (0.7)
Total	18 (100.0)	121 (100.0)	139 (100.0)
Yearly family income (grouped; USD)			
< $50,000	11 (61.1)	96 (79.3)	107 (77.0)
$50,000 to < $100,000	3 (16.7)	10 (8.3)	13 (9.4)
≥ $100,000	0 (0.0)	2 (1.7)	2 (1.4)
Missing	4 (22.2)	13 (10.7)	17 (12.2)
Total	18 (100.0)	121 (100.0)	139 (100.0)

BMI body mass index

BMI range for adults (kg/m^2): underweight: < 18.5, normal: 18.5 to < 25, overweight: 25 to < 30, obesity ≥ 30

BMI range for adolescents: underweight: BMI < the 5th percentile age, gender, and height

Normal: BMI ≥ the 5th percentile and < the 85th percentile for age, gender, and height

Overweight: BMI ≥ the 85th percentile but < the 95th percentile for age, gender, and height

Obese: BMI ≥ the 95th percentile for age, gender, and height

Table 3 Presence of atopic comorbidities

	Age group		
	Adolescents	Adults	Total
	n (%)	*n* (%)	*n* (%)
Total	18 (100.0)	121 (100.0)	139 (100.0)
Any	13 (72.2)	93 (76.9)	106 (76.3)
Allergic rhinitis	7 (38.9)	65 (53.7)	72 (51.8)
Allergic asthma	7 (38.9)	34 (28.1)	41 (29.5)
Food allergy	6 (33.3)	21 (17.4)	27 (19.4)
Allergic conjunctivitis	1 (5.6)	22 (18.2)	23 (16.5)
Chronic rhinosinusitis with nasal polyposis	0 (0.0)	5 (4.1)	5 (3.6)

14.6 ± 7.6. From the POEM single items, daily itch and disturbed sleep for ≥ 3 days were reported by about 40% of the patients for each item.

The impact of AD on the quality of life of patients was also assessed with the ADerm-IS in the domains of sleep, daily activities, and emotional state, confirming the moderate-to-severe rating of the disease, as also measured with the other tools (Table 6).

Treatment

The mean time from diagnosis to AD treatment initiation was 13.2 ± 13.0 years for any treatment and 14.2 ± 13.5 years for systemic treatment.

Practically all patients (99.3%) were receiving AD therapy: 87.7% were receiving topical therapy (30.9% alone), 44.2% were receiving systemic therapy, and 2.9% were receiving phototherapy. Of patients treated with topical therapy

Table 4 Presence of non-atopic comorbidity

	Age group		
	Adolescents	Adults	Total
	n (%)	*n* (%)	*n* (%)
Total	18 (100.0)	121 (100.0)	139 (100.0)
Any	4 (22.2)	42 (34.7)	46 (33.1)
Anxiety disorder	1 (5.6)	24 (19.8)	25 (18.0)
Hypertension	0 (0.0)	11 (9.1)	11 (7.9)
Depression	0 (0.0)	5 (4.1)	5 (3.6)
Alopecia areata	1 (5.6)	3 (2.5)	4 (2.9)
Cancer or history of cancer	0 (0.0)	3 (2.5)	3 (2.2)
Attention deficit hyperactivity disorder	1 (5.6)	1 (0.8)	2 (1.4)
Diabetes	0 (0.0)	2 (1.7)	2 (1.4)
Heart disease (coronary artery disease, angina, myocardial infarction, heart failure)	0 (0.0)	2 (1.7)	2 (1.4)
Autoimmune disease (rheumatoid arthritis, lupus erythematosus, multiple sclerosis, Sjögren's syndrome)	0 (0.0)	1 (0.8)	1 (0.7)
Obstructive sleep apnea	0 (0.0)	1 (0.8)	1 (0.7)
Osteoporosis	0 (0.0)	1 (0.8)	1 (0.7)
Vitiligo	1 (5.6)	0 (0.0)	1 (0.7)

Table 5 Combined EASI score

		Age group			
		Adolescents n (%)	Adults n (%)	Total n (%)	Group comparison: *p*-value (chi-squared test)
EASI score ≥ 16 and BSA ≥ 10.0% and vIGA-AD severity of AD ≥ 3	Yes	7 (38.9)	32 (26.4)	39 (28.1)	
	No	10 (55.6)	88 (72.7)	98 (70.5)	
	Missing	1 (5.6)	1 (0.8)	2 (1.4)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.2147
EASI score ≥ 16 and BSA ≥ 10.0% and vIGA-AD severity of AD ≥ 3 and worst pruritus NRS ≥ 4	Yes	4 (22.2)	31 (25.6)	35 (25.2)	
	No	2 (11.1)	88 (72.7)	90 (64.7)	
	Missing	12 (66.7)	2 (1.7)	14 (10.1)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.0306
EASI score > 21.0 and vIGA-AD severity of AD > 3 and BSA > 10%	Yes	3 (16.7)	18 (14.9)	21 (15.1)	
	No	14 (77.8)	102 (84.3)	116 (83.5)	
	Missing	1 (5.6)	1 (0.8)	2 (1.4)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.7768
EASI score ≥ 16.0 and DLQI/cDLQI ≥ 8 and BSA ≥ 10%	Yes	7 (38.9)	32 (26.4)	39 (28.1)	
	No	10 (55.6)	88 (72.7)	98 (70.5)	
	Missing	1 (5.6)	1 (0.8)	2 (1.4)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.2147

alone ($n = 43$; 31.2%), 27.9% were treated with low/mid potency TCS, and 51.2% were treated with high/ultra-high TCS or TCI.

Among the patients who were receiving systemic therapies ($n = 61$), the most frequently administered were dupilumab (37.7%), corticosteroids (34.4%), cyclosporine (21.3%), and methotrexate (14.8%). Figure 1 provides the details for all administered therapies.

Overall, when replying to the relevant questionnaire, one out of five (21.3%) patients perceived that their current treatment was not effective in controlling AD.

Healthcare Resource Utilization

In the 6 months prior to enrollment, 66.1% of patients had at least one healthcare visit (mean: 4.0 ± 3.6 visits), 51.3% had extra or unscheduled visits (mean: 2.5 ± 2.7 visits), and 10.1% had acute care visits. Patients mostly attended dermatology specialists (96.2%) and primary care physicians (26.9%).

Table 6 ADerm-IS scores

		Age group			
		Adolescents ***n*** **(%)**	**Adults** ***n*** **(%)**	**Total** ***n*** **(%)**	**Group comparison:** ***p*****-value (chi-squared test)**
Sleep domain score ≥ 12	Yes	3 (16.7)	53 (43.8)	56 (40.3)	
	No	4 (22.2)	67 (55.4)	71 (51.1)	
	Missing	11 (61.1)	1 (0.8)	12 (8.6)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.9459
Daily activities domain score ≥ 14	Yes	1 (5.6)	45 (37.2)	46 (33.1)	
	No	5 (27.8)	75 (62.0)	80 (57.6)	
	Missing	12 (66.7)	1 (0.8)	13 (9.4)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.3010
Emotional state domain score ≥ 11	Yes	4 (22.2)	56 (46.3)	60 (43.2)	
	No	3 (16.7)	64 (52.9)	67 (48.2)	
	Missing	11 (61.1)	1 (0.8)	12 (8.6)	
	Total	18 (100.0)	121 (100.0)	139 (100.0)	0.5894

Out-of-Pocket Expenses

The out-of-pocket mean monthly expenses and costs due to AD are shown in Fig. 2. Expenses significantly raised for the adolescents at US $172.86 ± 85.76 ($p = 0.0253$). This difference was mainly driven by the costs for everyday necessities (personal hygiene, clothing, washing powder, food or food supplements, sun products, cleaning products, bedding, and gloves).

The mean monthly expenses and costs due to AD as percentage of yearly family income for the study population were 0.94 ± 3.17%, and for 73.4% of the patients they represented < 5% of the yearly family income.

Productivity and Activity Impairment

For employed patients ($n = 79$), the mean overall work productivity impairment was 29.8 ± 27.0%, with an important part being due to presenteeism (Fig. 3).

Activity impairment was noted in almost one third of the patients (32.4 ± 27.7%). The impairment was numerically more important for the adolescents than for the adults ($p = 0.2437$) (Fig. 4).

DISCUSSION

The MEASURE-AD study aimed to better understand the burden of AD in several countries. This cluster subanalysis of Portuguese and Greek patients shows that AD has a significant burden, both clinical and financial, while further

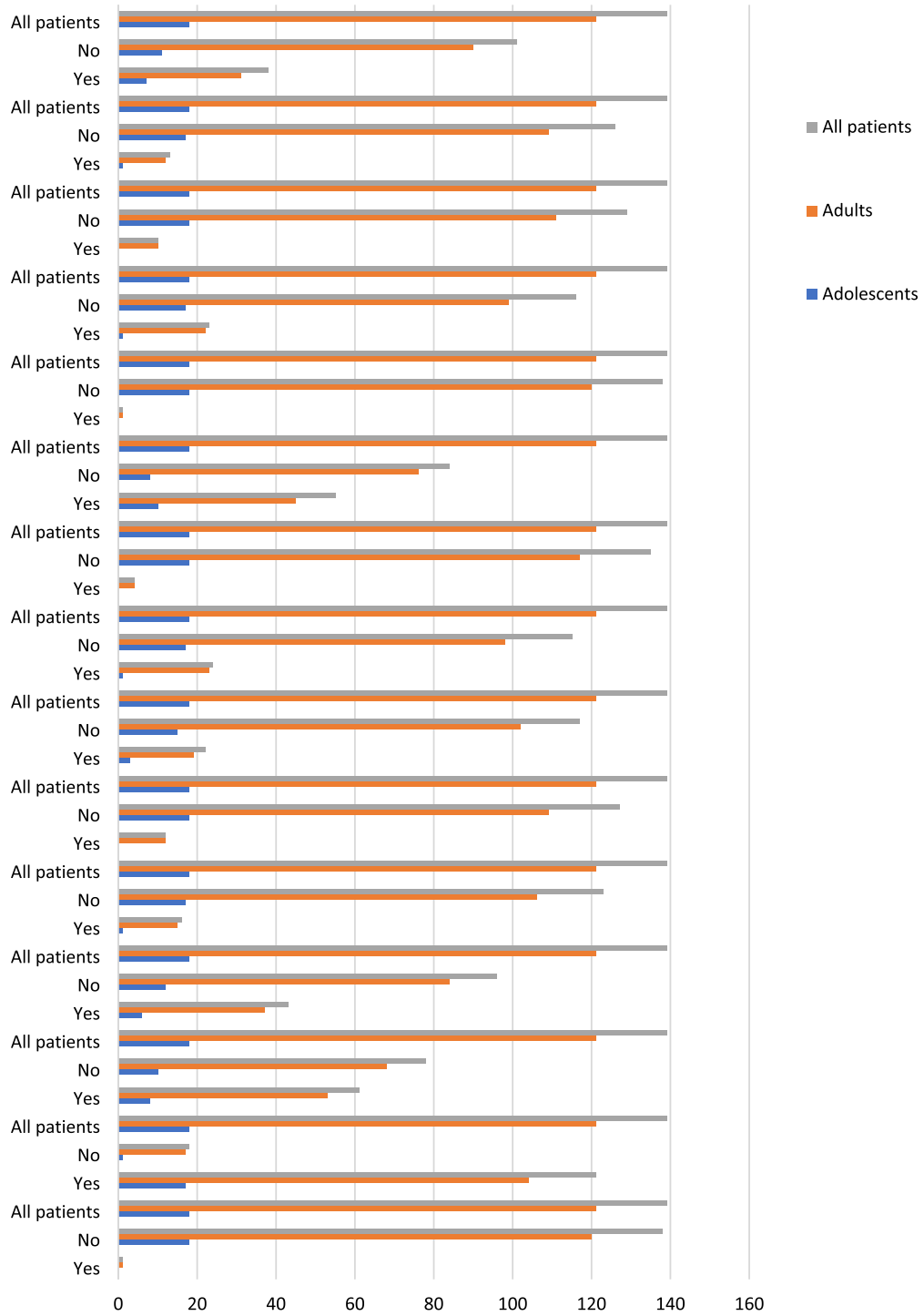

Fig. 1 Characterization of AD therapy at the time of the study; *AD* atopic dermatitis, *TCS* topical corticosteroids, *TCI* topical calcineurin inhibitors

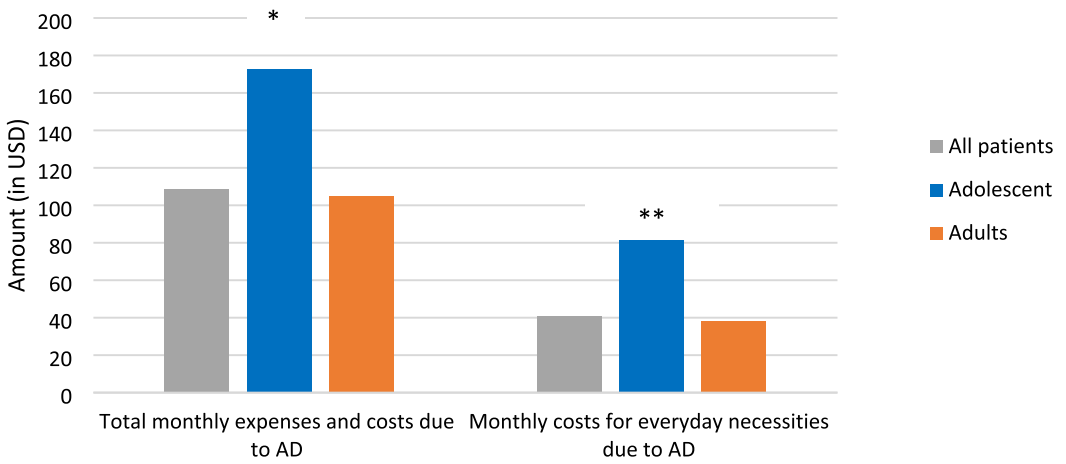

Fig. 2 Out-of-pocket mean monthly expenses and costs. *AD* atopic dermatitis; $^{*}p = 0.0253$ versus all patients, $^{**}p = 0.0086$ versus all patients

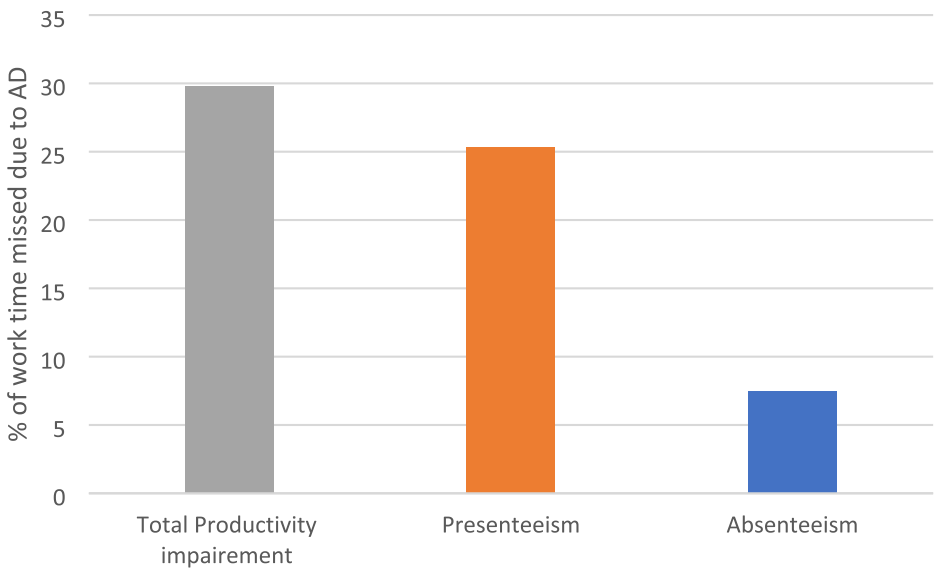

Fig. 3 Work productivity impairment due to AD; *AD* atopic dermatitis

enriching and confirming previous results of groups from both countries [24, 40, 41]. Indeed, the quality of life was reported by both groups to be importantly impacted in terms of duration and quality of sleep and social activities, while our study demonstrated an even higher impact [24, 37]. Similarly, productivity of patients was importantly impacted by the disease in a similar way to that reported by Gregoriou et al. [40].

The clinical profile of the patients showed moderate-to-severe disease, as evaluated by the SCORAD, EASI and vIGA-AD scales. It is rather surprising that, despite the long follow-up period, patients remained suboptimally controlled. In terms of clinical manifestations, one

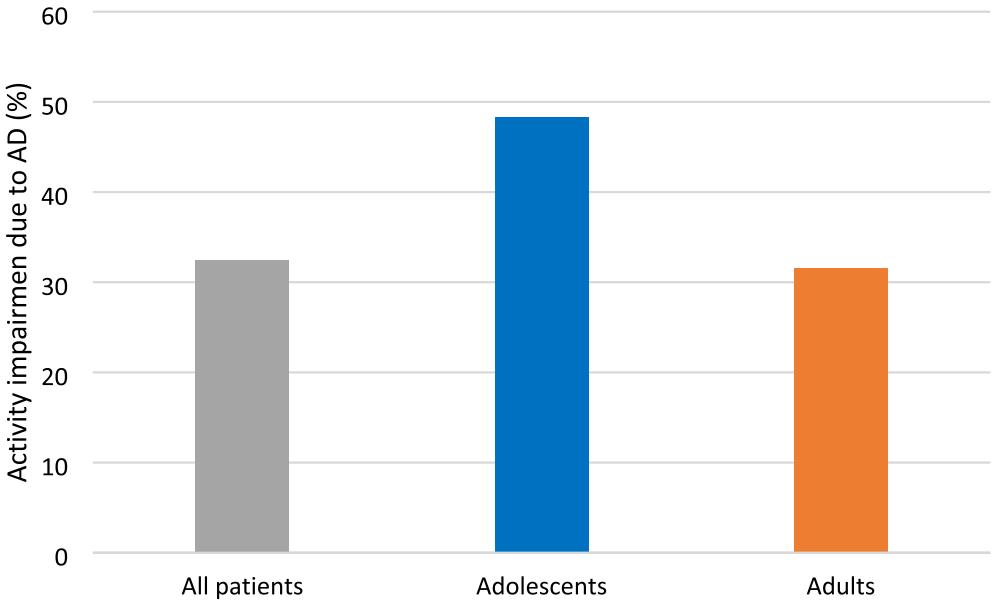

Fig. 4 Activity impairment due to AD; *AD* atopic dermatitis

third of the patients had more than five flares during the last 6 months prior to the enrollment, and 65.4% had a peak pruritus NRS score ≥ 4, which was indicative of moderate-to-severe disease with a duration of ≥ 6 h/day for 59.1% of patients. The severity of the symptomatology led approximately two out of three patients to report that the impact of AD on their quality of life was at least moderate, similar to what was observed in the global MEASURE-AD results (approximately 67% of adult patients), with itching being the key impacting symptom [22]. Importantly, approximately 24% and 33% of the patients presented depression and anxiety, respectively, possibly related to AD symptoms. Similar observations are described in literature [13, 41, 42].

The disease also affected patients' productivity, with a 30% work productivity impairment noted in the adult population, while the overall daily activity was impaired in both age groups.

Out-of-pocket expenses are important for people with AD and their families. In a study by Chovatiya et al., these expenses were US $600 on average annually, with 42% of individuals spending > US $1000 and 8.5% > US $5000 per year [43]. These expenses are even higher in case of polypharmacy, as they are almost double [16]. In a study across nine European countries, the extra yearly spending on everyday necessities was 927€ [44]. In our study, the yearly average expenses and costs were US $1304, 63% for health-related expenses and 37% for everyday necessities related to AD. It is important to note that adolescents required 65% higher expenses than the adults. When productivity impairment is combined to the increased out-of-pocket expenses, the overall impact at an individual but also at a societal level, renders evident that, outside the clinical context, effective treatment of AD is a necessity at an economic level as well.

Practically all patients were under treatment, with approximately 30% of the patients receiving topical treatment only, while systemic treatment was initiated on average 14 years after diagnosis. Here we report that almost half of the patients received systemic therapy (44.2%), similar, although lower, to that observed in the MEASURE-AD global results (55.9%) [22]. Considering the severity profile and clinical manifestations of AD, the treatment received may be considered suboptimal with inadequate control of symptoms, this being further supported by the fact that about 20% of the patients considered their treatment not effective in controlling their disease.

Until the approval of dupilumab (September 2017) [45], the only available treatment options included TCS and TCI, phototherapy, and conventional systemic immunosuppressors such as corticosteroids, cyclosporine, methotrexate, and azathioprine. Currently, we have innovative treatments that advance the therapeutic goals enabling a shift toward personalized treatment approaches with targeted systemic therapies without the addition of TCS and/or TCI [46].

Dupilumab, an effective monoclonal antibody targeting the IL-4/IL-13 pathway with an established safety profile, has been an important achievement in AD advanced systemic treatment [47]. Another two monoclonal antibodies, tralokinumab and lebrikizumab, have been recently approved by the European Medicines Agency (EMA) for the treatment of moderate-to-severe AD [8, 48] as well as a new class of therapeutics, Janus kinase (JAK) inhibitors, that modulate the activity of proinflammatory cytokines related to AD [47, 49]. JAK inhibitors have shown clinically relevant improvements in EASI score [46, 50], reduction of pruritus, and an established safety profile, with upadacitinib and abrocitinib appearing to be the most efficacious targeted systemic therapies across 12–16 weeks of therapy [46]. Still, some rare but serious adverse events can occur and should be taken into consideration for therapeutic decision-making. Therefore, a comprehensive evaluation of a patient's baseline risk factors for complications and comorbid diseases is critical in assessing the net benefit of JAK inhibitors on a case-by-case basis [51, 52]. Overall, in addition to efficacy, factors such as safety, benefit–risk, and patient preferences should also be considered when personalizing a patient's treatment plan.

Study limitations included inclusion criteria that selected only patients who were receiving or were candidates for systemic treatment, excluding patients who were controlled with topical therapies. The study was also conducted at the time when only one biologic therapy (dupilumab) and no JAK inhibitors were approved for AD. The study was not a population-based sample, and results may not be generalized to all cohorts. Patients without routine visits were not enrolled, and only patients treated by the investigators of this study were included. The study recruited participants from dermatology centers with experience; therefore, a bias toward the expert-center-based care cannot be excluded. In addition, results may not be representative of the experience from sites not using all treatment options. Because of this, we may be underestimating the burden of AD. Furthermore, this was a cross-sectional study, and patients with a wide variety of treatment statuses were included. Self-reported duration of sleep might also be an unreliable assessment. One additional limitation of our study is the exclusion of patients with well-controlled mild AD, which may limit generalizability of our findings.

CONCLUSIONS

The treatment options for AD are numerous, but the adequate treatment is not always administered in a timely manner. Management of AD should consider the individual clinical variability of the disease as well as the variable impact that it might have on the patient's quality of life [4]. Overall, these results suggest that a more individualized treatment strategy with novel advanced systemic therapies would benefit both patients and the society.

The burden of AD in patients from Portugal and Greece included in the MEASURE-AD study is important. Although patients have been followed by a dermatologist for a long period, a majority still have moderate-to-severe disease. Besides, despite the fact that approximately three out of four patients had been diagnosed with AD for more than 10 years, the mean time to receive their first systemic treatment was 14.2 years, while almost a third of the patients received only topical therapy.

The efficacy of the administered treatment was not at the desired level, with a third of patients having more than five flares during the last 6 months. In addition, 75% of patients reported that the impact of AD on their quality of life was at least moderate, with pruritus being a major aggravating factor. The productivity of the patients was similarly affected by the disease, resulting in increased absenteeism and presenteeism.

These results suggest that AD is undertreated in patients with moderate-to-severe disease from Portugal and Greece, and there is a need for a more individualized treatment strategy [53].

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Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis data sets) as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous independent scientific research and will be provided following review and approval of a research proposal, statistical analysis plan (SAP), and execution of a data sharing agreement (DSA). The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. Data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select 'Home'.

Declarations

Conflicts of Interest. Pedro Mendes-Bastos has received honoraria for acting as consultant/speaker/principal Investigator for AbbVie, Almirall, Amgen, Apogee, Biogen, CS Labs, Eli-Lilly, Evelo Biosciences, Janssen-Cilag, Leo-Pharma, L'Oreal, Novartis, Organon, Pfizer, Pierre Fabre, Regeneron, Sanofi, and Viatris. Elisavet Lazaridou has received honoraria for acting as a consultant and/or as a speaker for Abbvie, UCB, Novartis, Janssen, Pfizer, LEO Pharma, Amgen, Sanofi, Pharmaserve Lilly, Pierre Fabre, L'oreal, and Genesis Pharma. Elisavet Lazaridou served as an investigator in clinical trials supported by Abbvie, UCB, Janssen, Leo, Amgen, L'oreal, and Boehringer Ingelheim. Tiago Torres has received honoraria for acting as a consultant and/or as a speaker for Abbvie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers-Squibb,

Celgene, Janssen, LEO Pharma, Eli-Lilly, MSD, Mylan, Novartis, Pfizer, Sanofi Genzyme, Sandoz, Samsung-Bioepis, UCB, and Viatris. Tiago Torres is or has been a principal investigator in clinical trials supported by AbbVie, Amgen, Janssen, Novartis, and Sanofi. Tiago Torres is an Editorial Board member of Dermatology and Therapy. Tiago Torres was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Charalampos Aggelakopoulos has no conflicts of interest. Ioannis Katsantonis is or has been a principal investigator in clinical trials supported by AbbVie, UCB, Novartis, LEO Pharma, and Amgen. Pantelis Aronis has no conflicts of interest. Dimitrios Rigopoulos has received honoraria for acting as a consultant and/or as a speaker for AbbVie, Genesis Pharma, Amgen, UCB, Novartis, and LEO Pharma. Dimitrios Rigopoulos served as an investigator in clinical trials supported by AbbVie, Genesis Pharma, Amgen, UCB, and Novartis. Current affiliation of Dimitrios Rigopoulos is Hygeia Hospital, Kifisias Av. 151 23, Marousi, Athens, Greece. Filomena Azevedo has no conflicts of interest. Felicidade Santiago has no conflicts of interest. Current affiliation of Felicidade Santiago is Unidade Local de Saúde de Coimbra, Praceta Professor Mota Pinto, 3004–561 Coimbra, Portugal. Markos Papakonstantis served as an investigator and/or consultant or speaker for AbbVie, Faran, Janssen, LEO Pharma, Pharmaserve Lilly, Novartis, Pfizer, and UCB. Paulo Varela served as an investigator and/or consultant or speaker for Abbvie, Almirall, Boehringer, Janssen, Leo, Lilly, Pfizer, Sandoz, and Sanofi. Vera S. G. Ribeiro and Aikaterini Kollia are employees of AbbVie Pharmaceuticals. Evaggelia Papadavid has received honoraria for acting as a consultant and/or as a speaker for AbbVie, Janssen, UCB, Novartis, Pharmaserve Lilly, Amgen, Takeda, Recordati, and Pfizer. Evaggelia Papadavid served as an investigator in clinical trials supported by Helsinn, Recordati, Novartis, and Janssen.

Ethical Approval. This study received approval from the institutional review boards of all involved institutions. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects (or that person's parent or legal guardian) provided informed consent to participate in the study.

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