Dermatology Practical & Conceptual

Patient Burden and Impact of Moderate-to-Severe Atopic Dermatitis in the Spanish Healthcare System: The APOLO Cross-Sectional Study

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ABSTRACT **Introduction:** Atopic dermatitis (AD) is a chronic inflammatory condition associated with a significant physical, psychological, and economic burden. This study aimed to determine the multidimensional impact of AD on patients and the Spanish healthcare system.

Methods: The present multicenter descriptive cross-sectional study was conducted at 12 Spanish sites to detect clinical practice assessments and validated patient-reported measures.

Results: A total of 62 patients were included (54.8% males; mean age: 33.1 years). According to the validated Investigator Global Assessment scale for AD, 61.3% and 38.7% of patients had moderate and severe AD, respectively. AD involved a mean of 43.3% body surface area, with patients reporting a median of 4.0 flares in the past year. The mean Patient-Oriented Eczema Measure (POEM) questionnaire score was 19.8, indicating severe eczema. In addition, 57.1% of patients reported daily pain from scratching or skin inflammation. The mean Dermatology Life Quality Index (DLQI) was 14.3, showing a strong AD impact on patients' quality of life, positively correlated with severity, pruritus, and pain. AD also affected work productivity and sleep, with over 50% of patients reporting impairments in daily activities. Treatment patterns showed predominant use of topical corticosteroids (81.5%). Although no patient required hospitalization in the previous year, 25% resorted to alternative therapies/unlicensed products.

Conclusions: AD profoundly impacts patients' quality of life and entails high economic costs. This study emphasizes the need for more effective treatment strategies and an improved understanding of the AD burden to utilize public healthcare resources more efficiently.

Introduction

With a prevalence of 3–5% in adults and up to 20% in children, atopic dermatitis (AD) represents the most prevalent skin disease. AD onset occurs within the first year of life in 50–60% of patients, although it also affects adults [1,2]. Despite its relatively low mortality rate, AD can be associated with substantial morbidity and disability. Indeed, according to the Global Burden of Disease consortium, AD is ranked in the top 15 of all nonfatal diseases in terms of disability-adjusted life year (DALY) and has the highest DALY burden among all skin diseases [3].

AD typically undergoes remitting and relapsing episodes with painful flares. Consequently, successful management of the disease requires pharmacological treatment to relieve itching, pain, and flares as well as self-care practices to maintain a healthy epidermal barrier, thus reducing AD symptoms and preventing flare-ups [4].

Persistent itching of the skin, the hallmark of AD, interferes with daily activities, causes sleep disorders, and adversely impacts patients' quality of life [5]. Altogether, this makes AD a physical, emotional, and financial burden for patients. As it is primarily a childhood disease, family members are often affected by both the psychosocial and financial implications of AD [6]. Indirect costs of managing the disease, such as doctor's appointments, absences from work, school, or hospitalizations, also emerge as a burden on society [7,8].

Despite the importance of psychosocial well-being, the stigma, and the financial impact of AD on patients, these aspects have been poorly addressed in Spain. Data on patients' journey through the healthcare system and available treatments in clinical practice are also limited.

Objectives

This study aimed to provide an overview of the management and treatment of patients with moderate-to-severe AD under routine clinical practice in Spain. Our goal was to determine the burden of the disease on patients' quality of life and their households as well as the financial burden and the impact on the Spanish healthcare system.

Methods

Study Design and Patients

APOLO (AtoPic dermatitis - a crOss-sectionaL study on disease characteristics and impact On patients) was a multicenter descriptive cross-sectional study designed to identify the impact of moderate-to-severe AD on young and adult patients and its burden, conducted at 12 Spanish dermatology centers following the Declaration of Helsinki and European and local requirements. The study was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain). Written informed consent was obtained from all patients (or their legal guardians) before their inclusion.

Included in the study were consecutive patients ≥12 years of age with a diagnosis of AD with a severity level ≥3 according to the validated Investigator Global Assessment scale for AD (vIGA-AD) [9] who requested medical attention because of AD for the first time in those centers. Those who were participating in clinical trials at the time of recruitment or who had other active concomitant skin diseases that could interfere with the results (such as psoriasis and chronic urticaria) were excluded. Patient recruitment was conducted from May 2022 to September 2023. Data on routine medical practice were collected during a single visit of patients to their referral center (study visit).

Study Endpoints

The primary endpoint was the impact of moderate-to-severe AD on patients' health-related quality of life (HR-QoL), work productivity, sleep, household, and the symptoms of the disease. This endpoint was addressed through a series of validated scales and questionnaires completed by the patients at the study visit. The HR-QoL was assessed by the Dermatology Life Quality Index (DLQI) [10] and the 3-level version of the EuroQuol EQ-5D index (EQ-5D-3L) [11], while the Children's Dermatology Life Quality Index (CDLQI) [12] was used in patients under age 16 years. The impact of the disease on work productivity was evaluated by the Work Productivity and Activity Impairment Questionnaire (WPAI) [13], and sleep disturbances were evaluated using a visual analog scale (VAS) from 0 (absence of insomnia) to 10 (worst insomnia imaginable). The impact on households was only assessed in patients ≤16 years, by the Dermatitis Family Impact Questionnaire (DFI) [14]. Symptoms, pruritus, and pain associated with moderate-to-severe AD were evaluated by the Patient-Oriented Eczema Measure (POEM) [15], the Peak Pruritus Numerical Rating Scale (PP-NRS) [16], and a VAS from 0 (absence of pain) to 10 (worst unbearable pain), respectively.

Secondary endpoints included a description of patients' demographic and clinical characteristics, treatment patterns for AD, and the healthcare resources consumed. To achieve these objectives, a medical chart review of patient demographic and clinical data (including the body surface and areas affected by AD and disease severity, assessed by the investigator using the Eczema Area and Severity Index [EASI] [17]) was conducted, and treatments used currently and in the past for AD were gathered. The main characteristics of healthcare resources used were also collected, detailing the number of hospital visits, hospitalizations due to AD in the previous year, and patients' personal costs.

Exploratory objectives included evaluating possible associations between disease severity/pruritus/pain and HR-QoL.

Statistical Analysis

A descriptive statistical analysis was performed on the study variables, using measures of central tendency and dispersion (mean and standard deviation [SD], median and interquartile range [IQR]) for quantitative variables, and frequencies and valid percentages for qualitative variables. The association between variables was measured by the Spearman's correlation coefficient.

Missing data were not considered in the analyses. All hypothesis tests were bilateral, and significance was considered at $p<0.05$. All statistical analyses were conducted using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

A total of 71 patients with AD met the selection criteria and were enrolled in the study. Nine patients were excluded because of screening failure; therefore, 62 patients were assessable for statistical analyses. As shown in Table 1, the mean (SD) age was 33.1 (12.8) years old, and 54.8% were males. Family history of AD and other allergic diseases were present in 30.4% and 18.5% of the population, respectively. Most (90.3%) patients showed at least one concomitant disease, including a history of asthma (55.4%) and a history of allergic rhinitis (43.4%), among others.

According to the vIGA-AD, disease severity was classified as moderate in 61.3% of patients and severe in 38.7%. When assessed by the EASI, which also incorporates the extent of body surface area affected, the proportion of patients by disease severity was almost evenly distributed between moderate (50.0%) and severe (46.8%) AD, with 3.2% having very severe AD. Overall, the mean score on the EASI scale was 23.4 (12.2). The median (IQR) age at onset of AD was 3.0 (1.0-12.5) years of age. AD affected a mean of 43.3% (22.1) of the body surface, with 75.8% of patients having face involvement and 73.7% in skin folds. Patients reported a median of 4.0 (2.0-10.0) AD flares in the previous year (Table 2).

Impact of AD on Patients' HR-QoL, Work Productivity, Sleep, and Household

The POEM showed that most patients experienced itching daily (85.2%), with bleeding (37.7%), and cracked and peeled skin (47.5% and 55.7%) during the week before the study visit (Table S1). Overall, the mean POEM score was 19.8 (6.4), indicating a severe stage of eczema. On the PP-NRS, in which 10 indicates "the worst imaginable itch" during the previous 24 hours, the mean score for the study population was 7.8 (2.1) (Table 3).

Assessment of pain associated with the disease was available for 55 patients. Among them, 49 (89.1%) experienced pain because of eczema. As shown in Table 3, more than half (57.1%) of patients stated experiencing pain every day. The mean pain score on the VAS, considering the

Table 1. Characteristics of the Study Population.

Characteristics	Value
Demographics	
Age (years), mean (SD) [N]	33.1 (12.8) [62]
Sex (male), n (%) [N]	34 (54.8) [62]
Ethnicity (Caucasian), n (%) [N]	56 (91.8) [61]
BMI (kg/m^2), mean (SD) [N]	25.2 (4.7) [57]
Education level, n (%) [N]	
Primary	4 (7.7) [52]
Secondary	12 (23.1) [52]
Post-secondary (not tertiary)	3 (5.8) [52]
Short-cycle tertiary	7 (13.5) [52]
Tertiary or equivalent	16 (30.8) [52]
Master's, specialization, or equivalent	10 (19.2) [52]
Professional situation, n (%) [N]	
Employed	34 (57.6) [59]
Student	14 (23.7) [59]
Unemployed	6 (10.2) [59]
Self-employed	4 (6.8) [59]
Retired	1 (1.7) [59]
Clinical Information	
Family history of AD, n (%) [N]	17 (30.4) [56]
Family history of other allergic diseases, n (%) [N]	10 (18.5) [54]
Concomitant diseases (>20%)[¥], n (%) [N]	56 (90.3) [62]
History of asthma	31 (55.4) [56]
History of allergic rhinitis	26 (46.4) [56]
History of allergic conjunctivitis	19 (33.9) [56]
History of food allergy	19 (33.9) [56]
Anxiety disorder	18 (32.1) [56]
Contact dermatitis	16 (28.6) [56]
Smoking habit	14 (25.0) [56]

Abbreviations: AD: atopic dermatitis; BMI: body mass index; n: patients with event; N: number of patients with available data; SD: standard deviation. [¥]Multiple response. Percentages can add up to more than 100%.

Table 2. Data on AD in the Study Population.

Study parameter	Value
vIGA-AD, n (%) [N]	
Moderate	38 (61.3) [62]
Severe	24 (38.7) [62]
EASI score, mean (SD) [N]	23.4 (12.2) [62]
EASI severity (grouped), n (%) [N]	
Moderate	31 (50.0) [62]
Severe	29 (46.8) [62]
Very severe	2 (3.2) [62]
Age at AD onset (years), median (IQR) [N]	3.0 (1.0-12.5) [53]
Body surface affected by AD (%), mean (SD) [N]	43.3 (22.1) [54]
Body areas of special interest affected by AD[¥], n (%) [N]	
Face/neck	47 (75.8) [62]
Face: periocular	39 (83.0) [47]
Neck	35 (74.5) [47]
Face: perioral	27 (57.4) [47]
Face: other	27 (57.4) [47]
Intertriginous skin areas	42 (73.7) [57]
Hands	30 (100.0) [30]
Feet	17 (40.5) [30]
Number of flares in the previous year, median (IQR) [N]	4.0 (2.0-10.0) [43]

Abbreviations: AD: atopic dermatitis; EASI: Eczema Area and Severity Index; IQR: interquartile range; n: patients with event; N: number of patients with available data; SD: standard deviation; vIGA-AD: validated Investigator Global Assessment scale for Atopic Dermatitis. [¥]Multiple response. Percentages can add up to more than 100%.

pain experienced in the week before the study visit, was 5.7 (3.0). Patients reported that open wounds due to scratching (62.0%), skin redness and inflammation (56.0%), and fissures (48.0%) mainly caused the pain.

According to the DLQI score (mean [SD] = 14.3 [7.6]), the symptoms and pain associated with AD had a very large impact on the HR-QoL of patients. The most adversely affected aspects of patients' lives were their symptoms and feelings (4.4 [1.5]), followed by their daily (3.1 [2.0]) and leisure (2.4 [2.0]) activities. Spearman's correlation analyses showed a positive and statistically significant association between the DLQI, and the severity of the disease (p=0.017), pruritus (p=0.003), and pain (p=0.005) experienced by patients (Table 4).

Moreover, according to the EQ-5D-3L, 45.6% of patients expressed moderate pain or discomfort and 47.4% experienced moderately anxious or depressed (Table S2).

AD also affected patients' work productivity, as shown in Table 5. Despite not causing absenteeism due to AD in the previous seven days, patients reported a median of 50.0% (21.3-70.0) overall work impairment caused by the disease. Similarly, AD impacted patients' academic activity. Thirteen (25.0%) patients reported attending classes, with a median of 76.0% (30.0-79.0) overall classroom impairment caused by AD in the seven days before the study visit. The median percentage of impairment in daily activities was 55.0% (20.0-77.5), and sleep disturbances on the three nights before the study visit were moderate (mean [SD] VAS = 6.0 [3.1]).

Table 3. Symptoms of Patients with AD Assessed by the POEM Questionnaire, PP-NRS, and a Pain VAS.

Symptoms assessment	Value
Total POEM score, mean (SD) [N]	19.8 (6.4) [61]
POEM groups, n (%), N=61	
Mild	2 (3.3)
Moderate	17 (27.9)
Severe	28 (45.9)
Very severe	14 (23.0)
Total PP-NRS score, mean (SD) [N]	7.8 (2.1) [60]
Pain score (VAS), mean (SD) [N]	5.7 (3.0) [57]
Patients with pain, n (%) [N]	49 (89.1) [55]
Frequency of pain due to eczema or AD, n (%), N=49	
Every day	28 (57.1)
5–6 days a week	8 (16.3)
3–4 days a week	6 (12.2)
1–2 days a week	3 (6.1)
Less than once a week	4 (8.2)
Causes of pain due to eczema or AD[¥], n (%), N=50	
Open wounds caused by scratching	31 (62.0)
Red and inflamed skin	28 (56.0)
Small cracks in the skin (fissures)	24 (48.0)
Itching caused by creams or ointments	12 (24.0)

AD: atopic dermatitis; n, patients with event; N: number of patients with available data; POEM: Patient Oriented Eczema Measure; PP-NRS: Peak Pruritus Numerical Rating Scale; SD: standard deviation; VAS: visual analog scale. [¥]Multiple response. Percentages can add up to more than 100%.

Table 4. DLQI of Patients with AD.

DLQI	Value		
Total DLQI score, mean (SD) [N]	14.3 (7.6) [58]		
DLQI groups, n (%), N=58			
0 - 1: No effect at all on patient's life	2 (3.4)		
2 - 5: Small effect on patient's life	5 (8.6)		
6 - 10: Moderate effect on patient's life	13 (22.4)		
11 - 20: Very large effect on patient's life	24 (41.4)		
21 - 30: Extremely large effect on patient's life	14 (24.1)		
Score in DLQI dimensions, mean (SD) [N]			
Symptoms and feelings	4.4 (1.5) [56]		
Daily activities	3.1 (2.0) [58]		
Leisure	2.4 (2.0) [57]		
Work and school	1.6 (1.9) [57]		
Personal relationships	1.9 (2.0) [57]		
Treatment	1.1 (1.1) [58]		
Variables associated with DLQI	**Spearman's coefficient**	**p-value**	**N**
EASI	0.313	0.017	58
PP-NRS	0.383	0.003	57
Pain VAS	0.395	0.005	50

Abbreviations: DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; n: patients with event; N: number of patients with available data; PP-NRS: Peak Pruritus Numerical Rating Scale; SD: standard deviation; VAS: visual analog scale.

Treatments for AD

At the study visit, 54 (87.1%) patients received treatment for AD. The most commonly used treatments were topical corticosteroids (81.5%) and emollients (75.9%). Similarly, 59 (95.2%) patients had received at least one treatment for AD in the past, with almost all of them receiving topical corticosteroids (94.9%). After the study visit, treatment was planned for 60 (96.8%) patients. Physicians recommended emollients to 88.3% of patients and topical corticosteroids to 78.3% (Table 6).

Approximately 17–18% of patients also required a different treatment at the study visit and afterward for special body areas affected, mainly the face and periorbital area. Topical calcineurin inhibitors and topical corticosteroids were generally recommended in these circumstances (Table S3).

Burden on the Healthcare System

Most patients (86.9%) were referred to the participating centers by other healthcare professionals, mainly from primary care (50.9%), dermatology (31.6%), or other medical services (8.8%; clinical trial campaign, labor health, transplant unit, and so on). However, they were first diagnosed with AD by a pediatrician (40.7%), dermatologist (32.2%), or primary care physician (25.4%) (Figure 1).

Patients reported having visited other healthcare centers in the past, with primary care (78.7%) and dermatology (75.4%) being the services most frequently visited (Figure 1).

During the year before the study visit, the median number of AD-related visits to the pharmacy was 10.0 (4.0-15.0). The median number of visits to a dermatology-specialized center was 2.0 (0.0-4.0), while it was 0.0 (0.0-1.0) for emergencies. No patient required hospitalization in the previous year (Table S4).

Some patients needed complementary diagnostic tests, listed in Table S5.

Healthcare Costs Borne by Patients

The overall healthcare expenses borne by patients with AD are summarized in Table S6. Briefly, 63.0% of patients needed

Table 5. Impact of AD on Work Productivity and Sleep Disturbances Evaluated by the WPAI and a VAS, respectively.

Study parameter	Value
Patients currently employed, n (%) [N]	42 (68.9) [61]
Work productivity, median (IQR) [N]	
% work time missed due to AD (absenteeism)	0.0 (0.0-9.1) [35]
% impairment while working due to AD (presenteeism)	40.0 (20.0-70.0) [35]
% overall work impairment due to AD (absenteeism and presenteeism)	50.0 (21.3-70.0) [31]
Patients currently attending academic classes, n (%) [N]	13 (25.0) [52]
Academic activity, median (IQR) [N]	
% class time missed due to AD	0.0 (0.0-20.0) [7]
% impairment in the classroom due to AD	60.0 (25.0-70.0) [9]
% overall classroom impairment due to AD	76.0 (30.0-79.0) [7]
Daily activities, median (IQR) [N]	
% activity impairment due to AD	55.0 (20.0-77.5) [12]
Sleep disturbances score (VAS), mean (SD) [N]	6.0 (3.1) [59]

Abbreviations: AD: atopic dermatitis; n: patients with event; N: number of patients with available data; SD: standard deviation; VAS: visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

to travel to receive healthcare assistance, with a median cost of €10 (€4.50–20.00) in the month before the study visit.

In addition, during the year before the visit, 35.9% of patients invested €50-200 in acquiring products to better control the disease. Notably, 25% of patients reported having resorted to alternative therapies or unlicensed products, including homeopathy, emollients, parapharmacy creams and soaps, and natural supplements, among others. Patients spent a median of €120 (€11.30–187.50) on these products.

Those patients who were in treatment with emollients at the time of the study visit (or during the previous two weeks; Table 6) spent a mean of €40.10 (€30.5) a month on emollients.

Discussion

Estimating and understanding the burden of AD can help treatment decision-making as well as support public health policies, prioritize interventions, and allocate resources more effectively [18]. The APOLO study presents an overview of the profile and symptoms of real-life patients with moderate-to-severe AD managed and treated at Spanish dermatology-specialized centers; presented also are the associated physical, emotional, economic, and social burdens. This study shows that AD considerably impacted patients' quality of life, accompanied by impairments in work/academic activities, moderate sleep disturbances, and a significant burden on the Spanish healthcare system, especially in primary care and dermatology.

In this real-world study, we observed an evident impact of AD on patients' HR-QoL. According to the DLQI, nearly 65% of patients experienced a large/very large effect of AD on their lives. The mean DLQI was similar to or even higher than values reported in previous studies [19-21], supporting that HR-QoL is severely compromised in patients with moderate-to-severe AD. These results also align with the findings from two recent real-world APOLO sub-studies conducted in Greece and Portugal [22,23]. Moreover, our data confirm that greater disease severity impacts patients' HR-QoL more acutely, as previously demonstrated [21-24].

Itching is often the most commonly mentioned symptom for patients with AD [24]. In accordance, we observed that most patients experienced itching daily, together with high scores on the PP-NRS, and a severe eczema stage according to the POEM. This symptom may be followed by depression and anxiety observed in almost half of patients in the EQ-5D-3L and showed a positive association with the DLQI. These results are consistent with those previously described in the literature [23,25,26] and highlight the profound psychological impact of AD.

The present study also revealed moderate sleep disturbances due to AD. Lethargy and inability to concentrate are two of the main outcomes of sleep disturbance [27,28], which could explain the low absenteeism but percentages over 50% of work/classroom impairment; Civelek E. and collaborators also reported low school absenteeism in children with AD [29]. In addition, a European retrospective analysis of adult patients with moderate-severe AD showed absenteeism under 5%, although the overall work impairment was around 30% [25], differing from our results. These variations may be due to the higher DLQI values observed in our study.

In Europe, moderate-to-severe forms of AD are estimated to cost €30 billion annually [30]. Treatments, dermatology consultations, and hospitalizations are considered the major economic burden [31,32]. Unfortunately, we could not estimate the financial charges due to AD, although our data indicate that the main burden of this disease falls on dermatology and primary care, and on patients in terms of the high costs they bear.

Despite the severe symptoms experienced by patients with AD and the considerable impact on their lives, we observed

Table 6. Treatment Patterns.

Treatment[¥]	At study visit (in the two weeks before the visit) n (%), N=54	Received in the past n (%), N=59	Planned (after the visit) n (%), N=60
Topical corticosteroids	44 (81.5)	56 (94.9)	47 (78.3)
Daily use	23 (54.8)	-	36 (76.6)
High potency (in case of daily use)	11 (43.5)	-	17 (47.2)
Emollients	41 (75.9)	51 (86.4)	53 (88.3)
Topical calcineurin inhibitors	15 (27.8)	19 (32.2)	18 (30.0)
Tacrolimus	13 (24.1)	-	16 (26.7)
Pimecrolimus	2 (3.7)	-	2 (3.3)
Other treatments for AD	14 (25.9)	-	-
Antihistamines	10 (18.5)	29 (49.2)	3 (5.0)
Systemic antibiotics	1 (1.9)	8 (13.6)	3 (5.0)
Topical antibiotics	2 (3.7)	7 (11.9)	-
Alternative medicine	1 (1.9)	5 (8.5)	0 (0.0)
Systemic corticosteroids	13 (24.1)	32 (54.2)	14 (23.3)
*Treatment duration (days), mean (SD)**	*18.6 (25.2)*	-	-
Cycles in the last year, mean (SD)	-	*2.3 (2.8)*	-
Ciclosporin	6 (11.1)	12 (20.3)	15 (25.0)
Treatment duration (months), mean (SD)	*11 (7.7)*	-	-
Phototherapy	2 (3.7)	9 (15.3)	1 (1.7)
Systemic immunosuppressors	1 (1.9)	6 (10.2)	2 (3.3)
Methotrexate	1 (1.9)	4 (6.8)	2 (3.3)
Azathioprine	0 (0.0)	2 (3.4)	0 (0.0)
Antiviral	-	2 (3.4)	0 (0.0)
Dupilumab	0 (0.0)	1 (1.7)	6 (10.0)

Abbreviations: AD: atopic dermatitis; n: patients with event; N: number of patients with available data; SD: standard deviation. [¥]Multiple response. Percentages can add up to more than 100%. *N=11.

a relatively low use of systemic therapies in this population, likely attributable to patients attending a specialized center for the first time (as per established selection criteria). Systemic corticosteroids were prescribed in less than 25% of patients, a very similar proportion to that observed by Klein and colleagues [25]. Furthermore, dupilumab was only recommended to six patients after the study visit, despite its approval for moderate-to-severe AD in Spain in 2017. Treatment patterns in the Greek and Portuguese cohorts further support a historical reliance on topical therapies, which may now be evolving towards a more disease-specific approach [22,23]. In the present study, although the high use of emollients illustrated an attempt to better control the disease and prevent flare-ups, the overall treatment algorithm suggested suboptimal management of AD. Indeed, the use of alternative therapies or unlicensed products by 25% of patients, together with their associated costs, may reflect unmet treatment needs.

Limitations of this study include missing information on some variables due to the descriptive study nature. As the sample size was low, extrapolating the results might be challenging, although it effectively reflects the Spanish population with moderate-to-severe AD. Moreover, we could not include enough young patients (data not shown) and adequately contrast the data from this specific population.

Conclusions

Despite its limitations, the APOLO study provides insight into the characteristics and symptoms of a representative moderate-to-severe AD population. This study highlights the devastating impact of AD on patients' lives in a real-world scenario, with a significant effect on their HR-QoL, sleep disruptions, and work impairments, and the overwhelming financial burden on patients and the Spanish healthcare system.

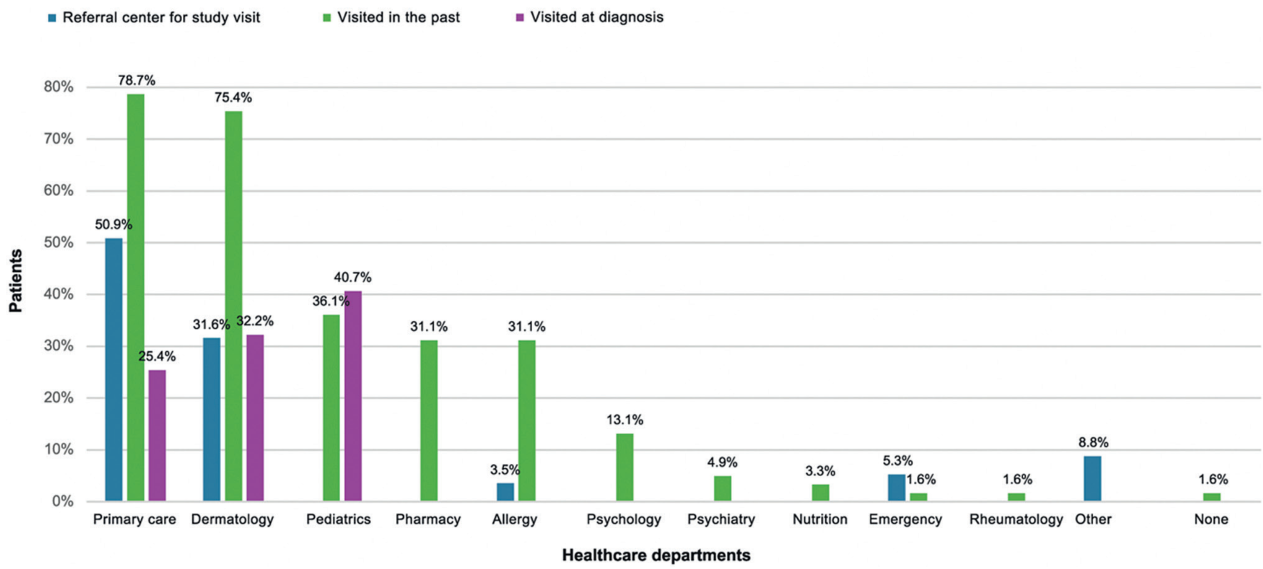

Figure 1. Healthcare departments most frequently visited by patients with AD

Ethics Approval: This study was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and in compliance with European and local requirements. Written informed consent was obtained from all patients (or their legal guardians) before their inclusion.

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