




The Economic and Psychosocial Comorbidity Burden Among Adults with Moderate-to-Severe Atopic Dermatitis in Europe: Analysis of a Cross-Sectional Survey

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a common inflammatory disease of the skin, which may have a substantial impact on patients' health-related quality of life (HRQoL). The aim of this study was to quantify the economic burden (direct and indirect costs) of moderate-to-severe AD and evaluate the prevalence and impact of psychosocial comorbidities among patients in the European Union-5 (France, Germany, Italy, Spain, and the UK).

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Methods: Data were analyzed from the 2017 EU5 National Health and Wellness Survey. Respondents with a physician diagnosis of AD/eczema who were considered to have moderate-to-severe AD based on a Dermatology Life Quality Index (DLQI) score ≥ 6 were included. Direct costs, indirect costs, and psychosocial comorbidities (sleep difficulties and anxiety based on self-report, depression based on the Patient Health Questionnaire-9) were reported descriptively. Generalized linear models were used to examine the relationship between psychosocial comorbidities and health outcomes (the Short Form-36 version 2 [SF-36v2], Euro-QoL 5-dimension 5-level, Work Productivity and Activity Impairment questionnaire, and healthcare resource utilization).

Results: Overall, 1014 patients were included in the analysis. Total annual direct costs ranged from €2242 to €6924 and total annual indirect costs ranged from €7277 to €14,236, depending on the level of disease severity. Sleep difficulties, anxiety, and depression were reported by 61.6%, 52.7%, and 75.8% of patients, respectively. These comorbidities were significantly associated with reduced physical and mental component summary scores from SF-36v2 and increased overall work impairment ($p < 0.05$ for all).

Conclusions: A significant economic burden was observed for patients with moderate-to-severe AD. Sleep difficulties, depression, and anxiety were observed in more than half of

moderate-to-severe AD patients and were significantly associated with decrements in HRQoL and with work-related impairment. Reducing the burden of these psychosocial comorbidities in AD could have significant benefit to patients and society.

Keywords: Anxiety; Atopic dermatitis; Depression; Health-related quality of life; Healthcare resource utilization; Sleep difficulties; Work impairment

Key Summary Points

Why carry out this study?

Atopic dermatitis (AD) is associated with a significant direct and indirect economic burden, and comorbidities associated with the disease can lead to poor health status, health-related quality of life (HRQoL), and work productivity.

Data on the overall costs, prevalence, and impact of psychosocial comorbidities of AD among European patients are limited.

This analysis quantified the economic impact (direct and indirect costs) and evaluated the prevalence and impact of psychosocial comorbidities (sleep difficulties, anxiety, and depression) in adult patients with moderate-to-severe AD in the European Union-5 (EU5) using data from the 2017 National Health and Wellness Survey.

What was learned from the study?

Moderate-to-severe AD resulted in significant indirect (up to €14,000 per patient per year) and direct (up to €7000 per patient per year) costs across the EU5.

Sleep difficulties, depression, and anxiety were observed in more than half of patients with moderate-to-severe AD and were significantly associated with decrements in HRQoL and work-related impairment.

DIGITAL FEATURES

This article is published with digital features to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12902486>.

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, and relapsing inflammatory disease that is characterized by intense itch (pruritus) and dry skin [1]. Affecting up to 20% of the population [2], AD has been found to have a substantial impact on health-related quality of life (HRQoL), particularly among patients with more severe disease [3, 4].

There is also a significant economic burden of AD in terms of direct medical costs (i.e., direct costs) and costs through lost work productivity (i.e., indirect costs). Several studies in the US that leveraged administrative claims databases have reported that direct annual costs range from \$15,000 to \$20,000 per patient for those with moderate-to-severe disease, with the largest share of costs attributed to outpatient visits [5, 6]. Data from European patients are limited; however, a Spanish registry study found that direct costs ranged from €2000 to €3500 per patient per year for patients with moderate-to-severe AD [7]. A study in The Netherlands found that patients with uncontrolled disease who were eligible for systemic therapy had annual per patient direct and indirect costs of €6993 and €13,702, respectively [8].

Itch can be particularly disruptive to sleep in patients with AD [9]. Sleep disruption, especially when combined with the social stigmatization of visible skin lesions, can lead to increased rates of depression, anxiety, and suicidality among patients with AD [10–12]. Data from the National Health and Nutrition Examination Survey indicated that patients with AD had nearly twice the odds of having depression relative to patients without AD and more than two- and five-times greater odds of having moderate and severe depression, respectively, relative to patients without AD [10].

The objectives of this study were to determine the economic burden (both direct and indirect costs) associated with moderate-to-severe AD in the European Union-5 (EU5; France, Germany, Italy, Spain, and the UK) and to estimate the prevalence of common psychosocial comorbidities (sleep difficulties, anxiety, and depression) among patients with moderate-to-severe AD. The presence and severity of these comorbidities were associated with a wide array of health outcomes, including HRQOL, work and activity impairment, and healthcare resource utilization. Collectively, these data can be used to better understand the impact that moderate-to-severe AD has on European patients, healthcare systems, and overall society to improve its management.

METHODS

Data Source

This study involves an analysis of the cross-sectional 2017 National Health and Wellness Survey (NHWS), an annual, cross-sectional, internet-based survey of adults (≥ 18 years) conducted across several countries. The protocol and study materials associated with the original fielding of the 2017 NHWS were reviewed by the Pearl Institutional Review Board (Indianapolis, IN, USA) and granted exemption status. The current study used the EU5 dataset ($N = 62,000$; France [$n = 15,000$], Germany [$n = 15,000$], Italy [$n = 10,000$], Spain [$n = 7,000$], and UK [$n = 15,000$]). Potential respondents to the NHWS were recruited through various online panels (e.g., Lightspeed Research) and were sampled in a random stratified manner to mimic the demographic distributions of each country's adult population based on the International Database of the United States Census [13].

Potential respondents received an email invitation to complete the survey. Respondents who provided informed consent electronically completed the survey, which took approximately 30–45 min. Respondents who completed the survey were compensated with points valued between \$5 and \$10 USD.

Sample

Respondents who completed the NHWS were included in the analyses if they self-reported a physician diagnosis of “atopic dermatitis” or “eczema” and scored ≥ 6 on the Dermatology Life Quality Index (DLQI), which suggested a “moderate” to “extremely large” effect on a patient's quality of life [14].

Measures

Demographics and Health History

Respondents answered several demographic questions, including country, age, sex, marital status, income, and employment status; they also reported general health history information, including height and weight used to calculate a body mass index category, comorbidities used to calculate a Charlson comorbidity index (CCI) [15], and the number of years diagnosed with AD.

Psychosocial Comorbidities

Respondents self-reported whether they experienced either “insomnia” or “sleep difficulties” in the past 12 months and reported the level of severity for each as “mild,” “moderate,” or “severe.” A severity of sleep difficulties variable was defined as the highest self-reported severity rating of either insomnia or sleep difficulties in the past 12 months (mild, moderate, or severe) with an extra category of “no sleep difficulties” reserved for respondents who did not report either condition. Respondents also self-reported whether they had experienced anxiety in the past 12 months. Finally, respondents completed the Patient Health Questionnaire-9 (PHQ-9) [16], a validated nine-item instrument used to assess the severity of depression (0–4, “none/minimal depression”; 5–9, “mild depression”; 10–14, “moderate depression”; 15–19, “moderately severe depression”; 20–27, “severe depression”) in the past 2 weeks.

Health Outcomes

The Short Form-36 version 2 (SF-36v2) [17], EuroQoL 5-dimension 5-level questionnaire (EQ-5D-5L) [18], and the Work Productivity and

Activity Impairment questionnaire-General Health version (WPAI-GH) [19] were all administered as part of the NHWS. The physical component summary (PCS) and mental component summary (MCS) scores from SF-36v2, which assess aspects of generic health status, were included in the study. The PCS and MCS scores are normalized, with the population mean and standard deviation set to 50 and 10, respectively; higher scores indicate better health status [17]. The EQ-5D-5L is a generic HRQoL measure that produces a health utility index score from 0 to 1, with higher scores indicating better HRQoL [18]. The WPAI-GH is a six-item validated tool to assess the impact of health on work and leisure activities. It includes four metrics: absenteeism (percentage of work time missed because of one's health in the past 7 days), presenteeism (percentage impairment experienced while at work in the past 7 days because of one's health), overall work impairment (combination of absenteeism and presenteeism), and activity impairment (percentage impairment in daily activities because of one's health in the past 7 days) [19]. Respondents also self-reported healthcare resource utilization (number of healthcare provider visits, emergency room visits, and hospitalizations) in the past 6 months.

Statistical Analyses

Demographic, health characteristics, and health outcome variables were reported descriptively using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. The economic burden from indirect costs was calculated using a human capital approach; the proportion of work time that was missed was multiplied by the average annual wage to arrive at the cost for the lost productivity. Specifically, the mean percentage of overall work impairment observed within each country and DLQI severity band was multiplied by the country-specific median annual wage rates in 2017 (the same year as the NHWS data collection) from Eurostat [20]. Due to small sample sizes at the country level in some cases, a combined EU5 calculation

was performed and reported. Direct costs were calculated by multiplying the number of healthcare resource use visits by two (to annualize them) and then by the unit costs for these events within each country (e.g., if there was a mean of 5 physician visits in the prior 6 months and the average physician visit cost was €50, then the total annual cost would be €500). Unit costs were inflation adjusted to 2017 costs using the harmonized indices of consumer prices from Eurostat [21–23]. Total direct costs were calculated as the sum of the costs of physician visits, emergency room visits, and hospitalizations, which were reported overall at the EU5 level and by individual countries.

The prevalence of psychosocial comorbidities among respondents with AD was reported descriptively using frequencies and percentages. Generalized linear models were used to examine the association between psychosocial comorbidity categories and each health outcome variable. For normally distributed outcomes (SF-36v2 component summary scores and EQ-5D-5L index scores), a normal distribution with an identity link function was used. For positively skewed variables (WPAI-GH scores and healthcare resource utilization), negative binomial distributions with a log-link function were used. All models controlled for age, sex, country, income, employment status, body mass index, CCI score, and presence of other atopic conditions. Adjusted means were reported (on the original metric of each variable) for each level of the comorbidity category. The reference category was set to be the lowest level of each psychosocial comorbidity. Statistical significance was based on $p < 0.05$ relative to this reference category.

RESULTS

Sample Characteristics and Prevalence of Psychosocial Comorbidities

A total of 1014 respondents in the EU5 met criteria for having moderate-to-severe AD and were included in the analyses. Demographic and health history differences across the DLQI severity bands (i.e., “moderate,” “very large,” or

“extremely large” effect on the patient’s quality of life) are reported in Table 1. The mean age of patients ranged from 39.7 to 42.3 years; patients were predominantly female (53.6–72.0%), with more than a third having been diagnosed with AD for ≥ 16 years (31.9–37.2%). The proportion of male patients increased with severity ($p < 0.05$) and a greater comorbidity burden, as measured by the CCI, also increased with severity ($p < 0.05$). No other differences were observed.

Overall Economic Burden

Overall work productivity and annualized healthcare resource use by country are presented in Table 2. Rates of overall work impairment ranged from 32.3% (UK) to 47.3% (Spain) among patients in the moderate DLQI severity band, from 33.2% (UK) to 58.9% (Spain) among patients in the very large effect DLQI severity band, and from 67.9% (UK) to 74.0% (Italy) in the extremely large DLQI severity band. Applying published country-specific median wage data to these overall work impairment figures, the total indirect costs for moderate-to-severe patients across the EU5 ranged from €7277 to €14,236, depending on the DLQI severity band (see Fig. 1). Individual country results were limited by small sample sizes, yet were as follows: France, €6490–€13,315; Germany, €8655–€13,813; Italy, €6824–€11,885; Spain, €7012–€10,681; and UK, €7685–€16,150.

With respect to direct healthcare costs, the number of emergency room visits and hospitalizations (except for hospitalizations in France) increased significantly along with severity (Table 2). Although there were numerical differences in healthcare provider visits across DLQI severity bands, these were not statistically significant (Table 2). Applying country-specific unit costs, the annualized per-patient direct costs across the EU5 ranged from €2242 (moderate DLQI severity band) to €6924 (extremely large DLQI severity band) (Fig. 1). Country-specific results were as follows: France, €2764–€6261; Germany, €3028–€9894; Italy, €885–€4304; Spain, €720–€4706 (Spain had a different pattern of direct costs across DLQI

bands compared with the EU5; the extremely large DLQI severity band had the lowest costs and the very large DLQI severity band had the highest costs); UK, €2397–€7055.

Prevalence and Impact of Psychosocial Comorbidities

Psychosocial comorbidities were common across the EU5 countries (Table 3). A total of 61.7% of patients reported some form of sleep difficulties (37.8% reported “moderate” or “severe” difficulties), 52.7% reported anxiety, and 75.9% reported some form of depression (23.8% reported “moderately severe” or “severe” depression). The patterns were largely similar across countries, with the exception of patients in Germany, who reported lower levels of anxiety (29.5%) compared with other countries (51.3% to 61.5%).

The presence and increasing severity of these psychosocial comorbidities was significantly associated with poorer health outcomes, even after adjusting for confounding factors (Table 4). Patients with moderate or severe sleep difficulties reported significantly worse MCS (36.4 and 33.1, respectively, vs. 42.9 for those without sleep difficulties) and PCS (40.0 and 40.6 vs. 42.9) and EQ-5D health utilities (0.52 and 0.46 vs. 0.66) compared with those without sleep difficulties (all $p < 0.05$). Similarly, patients with moderate or severe sleep difficulties reported significantly greater overall work impairment (61.7% and 69.7%, respectively, vs. 52.3% for those without sleep difficulties), greater activity impairment (63.6% and 65.1% vs. 47.7%), and more physician visits (12.2 and 14.3 vs. 9.2) (all $p < 0.05$). No differences were observed with respect to hospitalizations, and only patients with severe sleep difficulties reported significantly more emergency room visits compared with patients without sleep difficulties (1.05 vs. 0.63, $p < 0.05$). Patients with mild sleep difficulties were typically not statistically different from those without sleep difficulties across most health outcomes, with the exception of MCS and activity impairment.

Patients with anxiety reported significantly worse MCS (36.6 vs. 43.7) and EQ-5D health

Table 1 Demographics and baseline characteristics of patients with atopic dermatitis by Dermatology Life Quality Index severity bands

	Moderate effect (DLQI 6–10) (N = 597)	Very large effect (DLQI 11–20) (N = 348)	Extremely large effect (DLQI 21–30) (N = 69)	p value
Age, mean (SD)	42.3 (16.3)	40.3 (14.2)	39.7 (13.5)	< 0.0001
Female [<i>n</i> (%)]	430 (72.0)	235 (67.5)	37 (53.6)	< 0.0001
Country [<i>n</i> (%)]				
France	157 (26.3)	82 (23.6)	17 (24.6)	
Germany	98 (16.4)	68 (19.5)	17 (24.6)	
UK	177 (29.7)	83 (23.9)	23 (33.3)	< 0.0001
Italy	87 (14.6)	64 (18.4)	9 (13.0)	
Spain	78 (13.1)	51 (14.7)	3 (4.4)	
Married/living with partner [<i>n</i> (%)]	335 (56.1)	193 (55.5)	49 (71.0)	0.0432
University educated [<i>n</i> (%)]	276 (46.2)	168 (48.3)	37 (53.6)	0.0845
Currently employed [<i>n</i> (%)]	341 (57.1)	217 (62.4)	49 (71.0)	0.0008
Body mass index [<i>n</i> (%)]				
< 18.5 (underweight)	43 (7.2)	16 (4.6)	6 (8.7)	
18.5 to < 25 (normal weight)	238 (39.9)	146 (42.0)	23 (33.3)	
25 to < 30 (overweight)	145 (24.3)	91 (26.2)	14 (20.3)	< 0.0001
≥ 30 (obese)	126 (21.1)	79 (22.7)	24 (34.8)	
Missing/unknown	45 (7.5)	16 (4.6)	2 (2.9)	
Smoking status [<i>n</i> (%)]				
Currently smoke	189 (31.7)	110 (31.6)	30 (43.5)	
Former smoker	146 (24.5)	89 (25.6)	14 (20.3)	< 0.0001
Never smoked	262 (43.9)	149 (42.8)	25 (36.2)	
Alcohol consumption [<i>n</i> (%)]				
Currently drink	470 (78.7)	258 (74.1)	51 (73.9)	0.1979
Do not currently drink	127 (21.3)	90 (25.9)	18 (26.1)	
Charlson comorbidity index [<i>n</i> (%)]				
0	470 (78.7)	275 (79.0)	39 (56.5)	
1	69 (11.6)	35 (10.1)	18 (26.1)	
2	32 (5.4)	20 (5.8)	4 (5.8)	< 0.0001
≥ 3	26 (4.4)	18 (5.2)	8 (11.6)	

Table 1 continued

	Moderate effect (DLQI 6–10) (<i>N</i> = 597)	Very large effect (DLQI 11–20) (<i>N</i> = 348)	Extremely large effect (DLQI 21–30) (<i>N</i> = 69)	<i>p</i> value
Other atopic condition [<i>n</i> (%)]				
Allergic rhinitis and/or asthma	234 (39.2)	148 (42.5)	35 (50.7)	0.0057
Neither allergic rhinitis nor asthma	363 (60.8)	200 (57.5)	34 (49.3)	
Years since diagnosis of atopic dermatitis				
< 5 years	197 (33.0)	142 (40.8)	19 (27.5)	< 0.0001
6–10 years	89 (14.9)	50 (14.4)	13 (18.8)	
11–15 years	63 (10.6)	22 (6.3)	8 (11.6)	
≥ 16 years	222 (37.2)	111 (31.9)	25 (36.2)	
Missing/unknown	26 (4.4)	23 (6.6)	4 (5.8)	

DLQI Dermatology Life Quality Index

utilities (0.66 vs. 0.76) and higher levels of absenteeism (17.4% vs. 12.5%), presenteeism (42.5% vs. 35.1%), overall work impairment (49.3% vs. 39.9%), and activity impairment (49.8% vs. 41.6%) compared with patients who did not report anxiety (all $p < 0.05$). Although patients with anxiety also had a trend toward more healthcare resource use visits in the past 6 months, only the number of physician visits was significantly different (9.7 vs. 6.7, $p < 0.05$).

Patients with an increasing severity of depression (particularly moderate, moderately severe, and severe levels) exhibited significantly poorer outcomes with respect to MCS, PCS, EQ-5D health utilities, and all WPAI-GH metrics compared with patients without depression (Table 4). A similar pattern was observed for physician visits (all $p < 0.05$), although the number of emergency room visits was only significantly different between patients without depression and those with moderate depression (0.89 vs. 0.55, $p < 0.05$) and the number of hospitalizations was only significantly different between patients without depression and those with moderate (0.58 vs. 0.30, $p < 0.05$) and moderately severe depression (0.53 vs. 0.30, $p < 0.05$).

DISCUSSION

The results of this study suggest a significant economic burden for patients with moderate-to-severe AD across the EU5. Direct costs for patients with the highest AD severities can approach €7000 per patient per year. However, the indirect costs are notably higher (ranging from €7000 to €14,000) per patient per year and reflect the impact of the disease, its symptoms, and the sequelae that can affect patients' ability to be present and productive at work. Comparisons with the literature are difficult given the lack of data, but our direct-cost findings in patients in Spain are similar to those reported previously [7]. Furthermore, the results across the EU5 for both direct and indirect costs are similar to those reported in The Netherlands [8]. The results of this study are also similar to a cross-sectional study in Japan, which found that cost per adult patient with AD increased with disease severity [24]. These findings reaffirm the impact that AD, particularly moderate-to-severe AD, can have on the healthcare system and overall society. Proper management of AD has been shown to alleviate the work loss burden imposed by the disease, as shown by the results of clinical trials [25].

Table 2 Work productivity and healthcare resource use by Dermatology Life Quality Index severity band across EU5 countries

	Moderate effect (DLQI 6–10)	Very large effect (DLQI 11–20)	Extremely large effect (DLQI 21–30)	<i>p</i> value
France				
Number of patients	157	82	17	
Number employed	83	43	9	
	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i> value
Absenteeism % (WPAI-GH)	11.2 (25.0)	17.4 (27.0)	20.3 (19.5)	0.3146
Presenteeism % (WPAI-GH)	31.1 (25.0)	42.4 (28.0)	63.3 (26.0)	0.0008
Overall work impairment % (WPAI-GH)	33.6 (27.7)	47.9 (31.0)	69.0 (27.8)	0.0005
Healthcare provider visits	7.85 (8.00)	8.11 (10.11)	9.76 (7.81)	0.6911
Emergency room visits	0.50 (1.29)	0.73 (1.77)	1.88 (2.71)	0.0028
Hospitalizations	0.27 (0.59)	0.41 (0.92)	0.65 (1.41)	0.0964
Germany				
Number of patients	98	68	17	
Number employed	49	38	9	
	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i> value
Absenteeism % (WPAI-GH)	22.4 (32.6)	29.0 (35.7)	38.3 (21.6)	0.3517
Presenteeism % (WPAI-GH)	34.8 (26.1)	42.4 (25.9)	41.0 (28.9)	0.4239
Overall work impairment % (WPAI-GH)	40.4 (30.2)	52.1 (28.9)	64.4 (27.7)	0.0453
Healthcare provider visits	11.62 (9.75)	11.34 (11.15)	13.47 (12.75)	0.7559
Emergency room visits	0.28 (0.74)	0.34 (0.66)	0.88 (1.32)	0.014
Hospitalizations	0.28 (0.74)	0.34 (0.87)	1.12 (1.41)	0.0013
Italy				
Number of patients	87	64	9	
Number employed	56	43	8	
	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i> value
Absenteeism % (WPAI-GH)	14.2 (25.7)	14.0 (19.7)	17.6 (19.2)	0.9178
Presenteeism % (WPAI-GH)	39.6 (26.6)	43.3 (25.6)	70.0 (12.0)	0.0088
Overall work impairment % (WPAI-GH)	42.5 (29.3)	47.5 (27.9)	74.0 (13.2)	0.0141
Healthcare provider visits	9.41 (14.59)	8.11 (12.78)	11.11 (9.24)	0.7536
Emergency room visits	0.24 (0.55)	0.47 (0.84)	1.44 (1.51)	<.0001
Hospitalizations	0.08 (0.27)	0.19 (0.50)	0.78 (1.09)	<.0001

Table 2 continued

	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i> value
Spain				
Number of patients	78	51	3	
Number employed	45	35	1	
	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i> value
Absenteeism % (WPAI-GH)	7.3 (11.8)	15.3 (18.9)	9.0 (-)	0.0746
Presenteeism % (WPAI-GH)	43.5 (28.3)	53.1 (24.2)	70.0 (-)	0.1972
Overall work impairment % (WPAI-GH)	47.3 (28.9)	58.9 (26.2)	72.0 (-)	0.1453
Healthcare provider visits	7.08 (5.95)	9.75 (7.22)	9.00 (6.00)	0.0746
Emergency room visits	0.65 (1.07)	1.39 (1.42)	0.33 (0.58)	0.0029
Hospitalizations	0.09 (0.51)	0.47 (0.86)	0.00 (0.00)	0.0065
UK				
Number of patients	177	83	23	
Number employed	86	51	18	
	Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i> value
Absenteeism % (WPAI-GH)	10.9 (25.4)	14.9 (26.3)	23.9 (25.2)	0.1374
Presenteeism % (WPAI-GH)	29.5 (26.2)	28.5 (28.0)	60.6 (25.1)	<.0001
Overall work impairment % (WPAI-GH)	32.3 (28.6)	33.2 (31.5)	67.9 (21.2)	<.0001
Healthcare provider visits	6.55 (7.78)	6.18 (11.26)	5.87 (7.01)	0.9118
Emergency room visits	0.25 (0.73)	0.47 (0.98)	1.00 (1.76)	0.0009
Hospitalizations	0.21 (0.68)	0.18 (0.57)	0.87 (1.52)	0.0003

DLQI Dermatology Life Quality Index, *EUS* European Union 5, *WPAI-GH* Work Productivity and Activity Impairment-General Health questionnaire

This study also examined the prevalence of psychosocial comorbidities. Consistent with prior studies, we found that > 60% of patients experience some form of sleep difficulties [26]. However, our reported rates of anxiety (50%) and depression (75%, with nearly 25% of all patients reporting moderately severe or severe depression) were higher than in prior studies [27, 28]. The difference observed may be due to the population of the different studies. Many prior studies focused on the entire AD population rather than moderate-to-severe patients

specifically, and these results would suggest that the psychological burden is greater among those with more severe disease.

The results of this study also suggest that the presence and increasing severity of these comorbidities are associated with poorer outcomes, particularly in health status, HRQoL, and work productivity loss. The effects of these comorbidities on healthcare resource use were less clear; in general, the more severe manifestations were associated with more healthcare provider visits and, in some cases, emergency

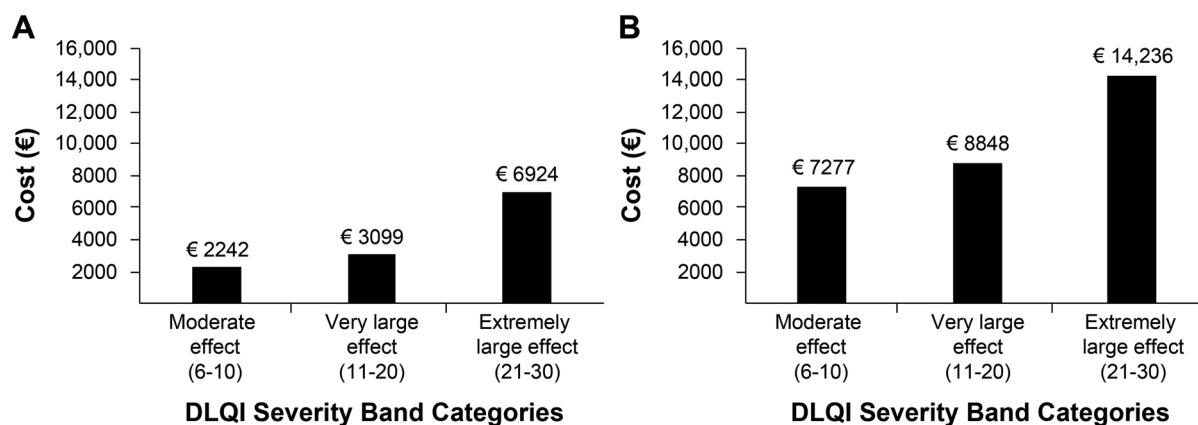


Fig. 1 Annual per patient direct (a) and indirect (b) costs across the EU5 by DLQI severity bands. *DLQI* Dermatology Life Quality Index

Table 3 Prevalence of psychosocial comorbidities among moderate-to-severe atopic dermatitis patients across EU5 countries

<i>n</i> (%)	France (<i>N</i> = 256)	Germany (<i>N</i> = 183)	Italy (<i>N</i> = 160)	Spain (<i>N</i> = 132)	UK (<i>N</i> = 283)	Total EU5 (<i>N</i> = 1014)
Severity of sleep difficulties						
No sleep difficulties	90 (35.2)	57 (31.1)	76 (47.5)	46 (34.8)	120 (42.4)	389 (38.4)
Mild	59 (23.0)	53 (29.0)	36 (22.5)	40 (30.3)	54 (19.1)	242 (23.9)
Moderate	73 (28.5)	55 (30.1)	40 (25.0)	33 (25.0)	85 (30.0)	286 (28.2)
Severe	34 (13.3)	18 (9.8)	8 (5.0)	13 (9.8)	24 (8.5)	97 (9.6)
Anxiety	147 (57.4)	54 (29.5)	82 (51.3)	77 (58.3)	174 (61.5)	534 (52.7)
Depression (PHQ-9)						
None-minimal (0–4)	69 (27.0)	35 (19.1)	40 (25.0)	33 (25.0)	68 (24.0)	245 (24.2)
Mild (5–9)	91 (35.5)	58 (31.7)	65 (40.6)	39 (29.5)	71 (25.1)	324 (32.0)
Moderate (10–14)	45 (17.6)	48 (26.2)	33 (20.6)	24 (18.2)	54 (19.1)	204 (20.1)
Moderately severe (15–19)	33 (12.9)	27 (14.8)	17 (10.6)	25 (18.9)	47 (16.6)	149 (14.7)
Severe (20–27)	18 (7.0)	15 (8.2)	5 (3.1)	11 (8.3)	43 (15.2)	92 (9.1)

EU5 European Union 5; PHQ-9 Patient Health Questionnaire-9

room visits and hospitalizations. However, these differences were not always statistically significant. This suggests these comorbidities predominantly exacerbate the HRQoL and

indirect cost burden rather than the direct cost burden.

Our findings suggest a large incremental burden for patients with psychosocial

Table 4 Adjusted health outcome means by comorbidity category across EU5 countries

Health outcome	Comorbidity										
	Sleep difficulties			Anxiety			Depression severity				
	No sleep difficulties	Mild	Moderate	Severe	No	Yes	Non-minimal	Mild	Moderate	Moderately severe	Severe
Mental component summary (SF-36v2)	42.9	38.0*	36.4*	33.1*	43.7	36.6*	47.1	41.1*	37.9*	34.7*	29.1*
Physical component summary (SF-36v2)	42.9	42.9	40.0*	40.6*	46.2	46.2	44.6	44.3	42.7*	41.9*	42.5*
Health utilities (EQ-5D-5L)	0.66	0.63	0.52*	0.46*	0.76	0.66*	0.76	0.70*	0.65*	0.56*	0.42*
Absenteeism % (WPAI-GH)	21.5	23.0	25.4	29.4*	12.5	17.4*	28.6	32.8	36.3*	40.5*	43.5*
Presenteeism % (WPAI-GH)	45.5	47.9	55.9*	59.4*	35.1	42.5*	36.3	40.0	52.0*	60.2*	62.3*
Overall work impairment % (WPAI-GH)	52.3	53.7	61.7*	69.7*	39.9	49.3*	47.8	51.8	65.6*	74.4*	74.7*
Activity impairment % (WPAI-GH)	47.7	53.3*	63.6*	65.1*	41.6	49.8*	37.4	44.9*	54.2*	61.8*	66.9*
Number of physician visits in past 6 months	9.2	10.0	12.2*	14.3*	6.7	9.7*	7.8	9.4*	11.2*	11.3*	14.5*
Number of emergency room visits in past 6 months	0.63	0.55	0.65	1.05*	0.45	0.51	0.55	0.70	0.89*	0.81	0.69
Number of hospitalizations in past 6 months	0.38	0.46	0.45	0.43	0.32	0.36	0.30	0.37	0.58*	0.53*	0.43

EQ-5D-5L EuroQoL 5-Dimensions 5-Level, *EU5* European Union 5, *SF-36v2* Short Form 36 version 2; *WPAI-GH* Work Productivity and Activity Impairment- General Health questionnaire

* $p < 0.05$ relative to reference categories of “no sleep difficulties,” “no anxiety,” and “none-minimal” depression

comorbidities. Prior studies have demonstrated that these comorbidities are more frequent among patients with less controlled disease [4] and that effective AD therapies can reduce the levels of anxiety, depression, and sleep disturbances [29]. Our study's results suggest that improved management of the psychosocial health of patients can have additional benefits for the healthcare system and society.

Limitations

The NHWS database consists solely of patient-reported information, without any verification (clinician or otherwise) of responses. Although self-report of AD has been found to be reliable [30], defining severity based on DLQI bands may not produce the same results as using treatment history, Eczema Area and Severity Index score, and/or percentage of body surface area affected, none of which were available in the database. The cost data were estimated using patient-reported information rather than medical claims, although it did align with published data using other methods. It should be noted that indirect costs included only work loss and direct costs included only physician visits, emergency room visits, and hospitalizations. Costs associated with other aspects of disease management were not included. Because of the cross-sectional nature of the data, any relationships uncovered in the study can only be viewed as associations because the presence and direction of causality cannot be known. Although the study relied upon multivariable models to rule out alternative explanations, it is possible other factors could explain the relationships observed here. Finally, the current sample was recruited from the NHWS, and although the broad demographic characteristics of the entire NHWS sample and those of each respective country were similar, the extent to which our specific AD sample is generalizable to the broader AD population is unclear.

CONCLUSIONS

Moderate-to-severe AD results in a significant indirect and direct cost burden across the EU5.

Psychosocial comorbidities (i.e., sleep difficulties, depression, and anxiety) were common, observed in more than half of moderate-to-severe AD patients, and significantly associated with decrements in HRQoL and significantly associated with work-related impairment. Reducing the burden of these psychosocial comorbidities in AD could have significant benefit for patients and society.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to a data use agreement between the National Health and Wellness Survey and the authors but are available from the National Health and Wellness Survey on reasonable request.

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