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THE BURDEN OF ATOPIC DERMATITIS IN ADULTS AND ADOLESCENTS

PhD thesis

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List of abbreviations

36-HF	36-Item Short Form Health Survey
AD	Atopic dermatitis
CADTH	Canadian Agency for Drugs and Technologies in Health
CEE	Central and Eastern Europe
CPI	Consumer Price Index
CRD	Centre for Reviews and Dissemination
DALYs	Disability-Adjusted Life Years
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EQ-5D	EuroQoL 5 Dimensions questionnaire
EUR	Euros
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GP	General Practitioner
GRADE	Grading of Recommendations Assessment
HADS	Hospital Anxiety and Depression Score
HTA	Health Technology Assessment
JAK	Janus kinase
KSA	Kingdom of Saudi Arabia
LFPR	Labor Force Participation Rate
NICE	National Institute for Health and Care Excellence
POEM	Patient-Oriented Eczema Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QALYs	Quality-adjusted Life Years
QoL	Quality of Life

RQ	Research question
SCORAD	SCORing Atopic Dermatitis tool
SF-36	Short Form 36 questionnaire
SLR	Systematic Literature Review
UAE	United Arab Emirates
USA	United States of America
USD	United States Dollar
UV	Ultraviolet
VAS	Visual Analog Scale

1. Introduction

1.1. Atopic dermatitis disease background

Atopic dermatitis (AD) is a chronic skin disease that affects both children and adults (1). AD typically can be simply manifested as an inflammatory skin condition causing unpleasant symptoms such as pruritus, itching, and swelling. In some cases, however, the disease can be more severe, resulting in painful flares (2). Due to its chronic nature, AD can lead to long term effects, such as cracked or scaly skin (2). Although these symptoms may seem mild, studies have confirmed that AD has a substantial impact, especially due to reducing patients' and caregivers' quality of life (QoL), and through productivity losses (3, 4).

AD predominantly manifests in early childhood and may either resolve during childhood or persist into adulthood. In some cases, AD first appears during adolescence or adulthood, referred to as adult-onset AD (5, 6). It is often referred to as a pediatric disease, as it more commonly affects children, therefore, most published studies focus on the burden on pediatrics (7). However, AD is also prevalent and significant in adults and adolescents (7, 8).

AD encompasses a range of severity levels, ranging from simple cases, that could typically be managed with emollients, to severe stages that are associated with painful symptoms and intensive treatments. Accurate diagnosis of disease severity stage is a key to determine the most appropriate treatment. Several scoring systems are commonly used to evaluate AD severity levels, such as EASI (Eczema Area and Severity Index) and SCORAD (SCORing Atopic Dermatitis) (9). These scoring systems evaluate the severity level through assessing the size of the affected area, the symptoms, and clinical signs. The scales for these scoring systems differ, making it challenging to directly compare their results from studies using different tools. Mapping tools have been developed to match the results of these scoring systems and allow comparability across different scoring systems (10, 11).

AD is often perceived as a simple non-fatal skin condition, which can lead to its deprioritization in healthcare resource allocation compared to other more severe diseases

(12). Although this seems logic, when quantitatively comparing AD's burden to other diseases, it is associated with a significant burden that warrants efficient mitigation (13).

1.2. Epidemiology of AD

AD imposes a considerable burden, mainly due to the large number of patients affected globally (14). A recent study by Tian et al. published in 2023 estimated the global epidemiology of AD through a systematic analysis and modelling techniques. This study estimated the prevalence rate of AD as 4.0% in children and 2.0% in adults globally, corresponding to 102.7 million children and 101.27 million adults, respectively (15). While these numbers look alarmingly high, the study reported that these values lack 41.5% of the countries worldwide, indicating that the actual number of patients is even higher.

Unlike several recent studies reporting data for AD prevalence (16, 17), few studies focused on the incidence of AD (18). Based on a systematic literature review results, incidence of AD ranged from 10.2– 95.6 cases per 1,000 person-years (19). However, all these values were reported from European countries. Global epidemiological values might differ due to the significant difference of the disease by region and climate (15).

Climate significantly affects the epidemiology and symptoms of AD. Humidity, temperature, ultraviolet (UV) exposure, and climate change are among factors that affect AD's prevalence and symptoms (20). The relation between these factors and AD is complicated. For example, AD aggravates in regions with dry weather, due to skin dehydration. Interestingly, AD can also manifest in regions with high humidity, as excessive moisture may promote skin irritation (21). Therefore, prevalence values, and severity levels differ significantly between different geographical regions, and even within different regions in a country (15, 20).

1.3. Burden of disease studies

Burden of disease studies are essential to understanding the impact of diseases on the society. These studies include three primary domains: clinical, humanistic, and economic burdens, each consisting of several interconnected components (22, 23). Some of these components overlap across domains, making it challenging to clearly distinguish between them (24).

Clinical burden usually refers to the effect of a disease on mortality and morbidity, including its associated signs, symptoms, severity, survival and complications (23, 25).

Humanistic burden refers to the effects of a disease on QoL, which is defined as the degree to which an individual is healthy, comfortable, and able to participate in or enjoy life events (26). To quantitatively measure the value that individuals place on specific health states, QoL is often represented by a utility score (27). Utility scores range from 0 to 1, where 0 represents death and 1 represents perfect health (28). In severe cases, utility scores can even reach negative values, reflecting health states perceived as "worse than death" (29).

Humanistic burden is commonly measured in disability-adjusted life years (DALYs). DALYs are defined as the sum of the years of life lost due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population (30). Humanistic burden can also be measured as loss in quality-adjusted life years (QALYs). QALYs are calculated by combining utility scores with the duration spent in a given health state. QALYs help to quantify the benefits of healthcare interventions in terms of both survival and QoL, and are widely used for evaluating healthcare interventions (31).

Economic burden refers to the costs incurred due to the disease, either directly or indirectly. Its two main components direct and indirect costs (32). Direct medical costs of the disease include costs of medications, hospitalization and outpatient visits (33), while indirect costs are represented through productivity loss, which may occur due to absenteeism or presenteeism of patients or their caregivers. Absenteeism is defined as the numbers of days absent from work or school, and presenteeism is defined as the number or proportion of days present at work or school but not productive due to the disease (34).

The outcomes of burden of disease studies help decision-makers to take evidence-informed decisions regarding treatment strategies, resource allocation, and public health policies (35). Therefore, they could help to optimally prioritise interventions by highlighting where the greatest need exists (22).

With the rising healthcare costs globally, health technology assessment (HTA) has gained more importance among healthcare decision makers (36). HTA evaluates the value and cost-

effectiveness of health technologies, such as drugs, devices, and procedures, to improve the uptake of cost-effective health technologies. This ensures the optimal use of resources that are being spent (37). Effective HTA implementation requires robust data, with burden of disease studies serving as a crucial source of this data, such as disease prevalence, cost of treatment, and lost resources. Using burden of disease studies' findings, decisionmakers can allocate the resources among disease areas efficiently to maximize health benefits (22).

Among all burden of disease studies conducted, those that provide quantitative values and that provide country-specific data about the burden of disease are the most useful from the perspective of decisionmakers (38, 39). Additionally, only a few extend their findings to offer actionable recommendations aimed at reducing this burden (40). For a more comprehensive approach, a burden of disease study could be complemented by an additional study, or an extension to identify effective strategies that help mitigating the disease burden.

These actionable strategies might span various domains, based on each disease. Examples of these domains include adjustments to the treatment protocol, adjustments to treatment guidelines, allocating specific resources, improving public awareness, and enhancing capacity building programs, among others (41). These actions should be tailored for each country or setting, and should be validated with local experts, as different actions may result in distinct effects within several countries (42).

Beyond the obvious burden of a disease, represented in its direct medical costs, it is essential to evaluate other hidden burden components of a disease to accurately evaluate its true impact. These include less tangible components, such as reduced QoL and productivity loss, which are often more challenging to measure (43).

Studying the burden of a disease is essential to measure its impact on the individuals and society, that usually extend beyond its direct medical costs (33). This understanding of the disease burden can help mitigating the burden through resource allocation towards this disease, improving awareness, improving care for patients and ultimately better QoL.

1.4. The burden of AD

The significant burden of AD stems from multiple factors, including its high prevalence, its impact on QoL of both patients and caregivers, its psychosocial effects, productivity losses, and the considerable cost of treatments, especially in severe cases (44, 45).

Concerning humanistic burden, the Global Burden of Disease (GBD) study provides extensive data about the estimated AD DALYs stratified by age groups and regions (14). Additionally, it provides an online results tool that allows users to tailor disease burden data summaries stratified by country, gender, age group (46). The study reports that AD accounted for 0.36% of the total DALYs lost globally among 359 diseases. It ranked 59th for age-standardized global DALY rate, 15th among non-fatal diseases, and 1st among skin diseases.

These values were calculated using an estimated global prevalence rate of 2,690 patients per 100,000 persons. The GBD study, while providing comprehensive data on disease burden components, acknowledges its methodological limitations. These include constraints such as reliance on verbal data, outdated census values, and incomplete datasets (39). Despite these limitations, the reported values for AD remain alarmingly high for a non-fatal skin disease.

In 2017, AD accounted for 123 age-standardized DALYs per 100,000 persons globally, exceeding common skin diseases such as psoriasis, urticaria, and scabies (70, 68, and 60 DALYs, respectively) (14). Even when compared to more serious diseases, AD demonstrates an unexpectedly high burden, with around 9 million DALYs. This huge burden, largely driven by high prevalence, ranked AD above more severe conditions such as measles and upper respiratory tract infections (8.2 and 6.3 million DALYs, respectively) (47).

AD is associated with a significant impairment in QoL (48, 49). QoL is considered a patient-reported outcome (PRO) because it is evaluated using tools and questionnaires completed by the patients. These tools are referred to as patient reported outcome measures (PROMs). Various studies evaluating QoL in AD patients use different PROMs (50), each designed to assess QoL through a specific scale. Some of these tools are generic, such as European QoL-5 Dimension (EQ-5D) index and EQ-5D visual analog scale (EQ-5D VAS) (48, 49, 51). These generic questionnaires can measure QoL for various diseases, but lack disease specific

criteria (52). EQ-5D index questionnaire provides a five-digit health state profile that represents the patient's health status based on five health domains: mobility, self-care, usual activities, pain, and anxiety or depression, while EQ-VAS score records the patients' own assessment of their overall QoL on a scale (51).

AD patients' QoL can be also assessed using disease-specific questionnaires such as the Dermatology Life Quality Index (DLQI) (48, 49). The DLQI is a 10-item questionnaire assessing QoL impairment due to dermatological diseases (53). These disease-specific questionnaires are able to capture disease specific improvements in patients, such as the size of the affected area, but lack comparability among other diseases (52).

A study by Reed et al. supports the hypothesis that the burden of AD is probably higher than commonly recognized (54). Their study explores the clinical and humanistic burdens of AD, revealing that it significantly reduces patients' QoL, and presents considerable challenges to parents and caregivers managing the disease. Additionally, the study highlights that psychological effects and sleep disturbances contribute substantially to the disease burden. Notably, among 36 skin diseases assessed, AD ranked second in QoL impairment based on DLQI scores. The average DLQI score for AD was 12.2, second only to hirsutism, which had an average score of 12.8 (54, 55).

Several studies emphasized the importance of assessing the burden of AD on caregivers, demonstrating its significant contribution to the overall disease burden. However, these studies mainly focus on caregivers for children with AD (54, 56). In contrast, caregivers burden appears to be minimal for adult and adolescent patients. This may be due to that the primary responsibilities for caregivers of an AD child involve managing medications and waking up at night to help with flare-ups, affecting caregivers' QoL and productivity (57). For older patients, however, it seems that the burden shifts predominantly to the patients, while the burden on caregivers becomes limited (58).

Concerning economic burden, a recent study explored the economic impact of AD in United States of America (USA) (59), showing a substantial economic burden that exceeds 5 billion USD annually, including both direct and indirect costs. The study emphasized that indirect

costs constitute a large proportion of the total economic impact, as supported by findings from multiple studies. It also highlighted the importance of economic burden of disease studies in informing decisionmakers (59). These findings align with Drucker et al.'s study which reported the economic burden of AD in USA, emphasizing its substantial economic impact, impact on QoL, and its negative social effects (60).

In Europe, Augustin et al. estimated the total economic impact of moderate-severe eczema as 30 billion EUR annually, excluding the humanistic burden component. This included 15.2 billion EUR as indirect costs, 10.1 billion EUR as direct medical costs and 4.7 billion EUR as direct non-medical costs. The study reported that including humanistic burden can further increase the total economic impact of AD in Europe (61).

There are several treatments available for AD for different levels of disease severity, ranging from simple inexpensive emollients and topical corticosteroids, to phototherapy sessions, novel monoclonal antibodies and Janus kinase (JAK) inhibitors. These novel treatment modalities create an additional financial burden on healthcare systems to treat AD patients with the most advanced and effective therapies (62).

1.5. Scarcity of studies that quantitatively evaluate burden of disease components

As shown above, several studies and reports have explored the disease burden of AD. However, most of these studies explore the specific aspects of the burden, such as clinical burden, DALYs, or economic impact (14, 18, 39). Most burden of disease studies do not provide sufficient quantitative values of various components that would help decisionmakers take evidence-informed decisions. Furthermore, since AD is mostly recognized as a childhood disease (7), studies that quantify its burden predominantly focus on children, while there is scarcity regarding studies discussing the disease in older patients (63).

Although these studies seem to comprehensively cover the burden of AD topic, there is still scarcity of studies that quantify different components of the burden in adult and adolescent patients. Additionally, studies that study the burden in these populations don't provide solutions or actionable interventions to mitigate the burden of the disease.

2. Objectives

Through a comprehensive approach, the studies we conducted aimed to estimate the clinical and humanistic burdens of AD in adults and adolescents globally, to provide quantitative values for the economic and humanistic burdens of the disease in certain countries, to estimate the value of the hidden burden components, and to provide potential solutions to mitigate the disease burden. The ultimate goal of the whole research is to assist decision makers take efficient decisions towards mitigating the disease burden of AD in adults and adolescents.

Based on these aims, the following research questions (RQ) were formulated:

- RQ1: What is the clinical, humanistic and economic burden of AD in adults and adolescents globally?
- RQ2: What is the humanistic and economic burden of AD for in adult and adolescent patients in major countries in the Middle East and Africa (MEA) region?
- RQ3: What is the monetary value of the hidden burden of AD in in adult and adolescent patients in Central and Eastern European (CEE) countries?
- RQ4: What actions could be recommended to mitigate the burden of AD?

The findings of this research aim to support decision makers and budget holders responsible for healthcare resource allocation. By providing quantitative burden of disease values, the evidence can guide more efficient and impactful distribution of healthcare resources.

In each country, entities responsible for reallocating resources may include:

- Representatives from the Ministry of Health;
- Members of HTA bodies;
- Health Insurance authorities or payer.

Ideally, these stakeholders should interpret the burden of disease study results and align their funding priorities with the relative disease impact, thereby maximizing the value of health expenditure.

3. Methods

3.1. **Overview about the studies conducted**

To understand the burden of AD, we conducted several studies. First, we conducted a systematic literature review (SLR) to summarize and quantify the clinical, economic, and humanistic burden of AD in adults and adolescents globally. Next, we provided data for specific countries and regions presenting quantitative values for different burden components. These included a study assessing the economic and humanistic burden of AD in adults and adolescents in the MEA region (focusing on the major countries), and a study aiming to quantitatively investigate the hidden burden components of AD for adults and adolescents in CEE countries. Finally, we presented a study to show potential expert recommendations for mitigating the burden of AD.

The selection of MEA and CEE regions reflects the PhD candidate's (BE) professional and academic affiliations. Specifically, the candidate resides and works in the MEA region, while being enrolled in a PhD program in the CEE region. Importantly, both regions exhibit relevant contextual similarities that justify their joint assessment. These include diverse economic and social structures across countries, evolving HTA systems, and limited availability of local data necessary to inform efficient resource allocation. Furthermore, both regions face a high unmet need for structured burden-of-disease evidence to support informed policy decisions.

Collectively, these studies are directed towards healthcare decisionmakers, to provide quantitative values of the disease burden complemented with potential solutions for reducing the burden, to be able to take evidence-informed decisions.

Each of those studies were undertaken by a research team. The PhD candidate (BE) was part of the team in each study and had a substantial role in all steps. The exact contribution of the PhD candidate is elaborated in the methodology section of each respective study.

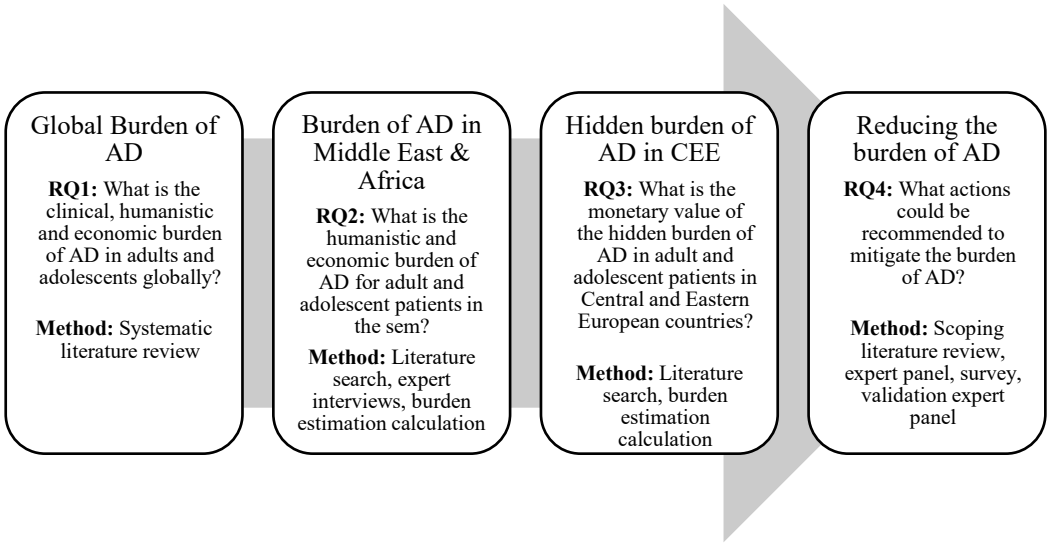

Figure 1 Research questions answered by each study

AD: Atopic dermatitis; CEE: Central and Eastern Europe

Figure 1 above provides an overview of the studies conducted, highlighting the research questions addressed by each, and summarizing the methodologies employed.

3.2. **Systematic literature review on the burden of AD (Methods related to RQ1)**

3.2.1. Aim of the systematic literature review

We conducted an SLR to summarize and quantify the clinical, economic, and humanistic burden of AD in adults and adolescents. The SLR was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRSIMA) guidelines for reporting SLRs (64).

We defined the Population, Interventions, Comparators, Outcomes, and Study designs (PICOS) of the included studies in this SLR as follows:

- Population (P): Adults and adolescents aged 10 years or older diagnosed with AD.
- Interventions (I) or Comparators (C): No specific restrictions were applied.
- Outcomes (O): any burden of disease components including clinical, humanistic, and economic burden data.

- Study designs (S): Observational and interventional studies, systematic reviews, and economic evaluations. Clinical trials were excluded to ensure the burden captured reflects real-world data rather than controlled conditions.

3.2.2. Search strategy and databases

We searched PubMed, Scopus, the Cochrane Library, the Centre for Reviews and Dissemination (CRD), and EconPapers for studies including relevant data. In addition, we reviewed grey literature sources including the ISPOR Presentations Database, as well as the websites of health technology assessment agencies such as the National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH). A short summary of these databases is presented in Supplementary Table S1.

The search string was based on two domains: Atopic dermatitis' and 'Burden of disease'. Synonyms for both domains were used to search all databases for studies published over the previous ten years. The search was conducted on 3 December 2020, and the timeframe was limited to studies published from 1 January 2011. Supplementary Table S2 shows the detailed search terms and number of hits in each database. The PhD candidate (BE) conducted the search in collaboration with the research team members.

3.2.3. Title and abstract screening

First, the search hits were deduplicated using EndNote software (version X9) and followed by a manual deduplication process by researchers during the title and abstract screening phase. Double blinded title and abstract screening was conducted by two independent researchers for each study to assess its eligibility for full text screening. The PhD candidate (BE) was one of the independent reviewers. Any conflicts between the researchers were resolved by a senior reviewer, including the PhD candidate (BE) for the conflicts that did not include him, while conflicts including him were resolved by another senior reviewer. The title and abstract exclusion criteria were:

1. duplicates,
2. no English abstract,
3. published before 1 January 2011,

4. letters, editorial, case reports, non-systematic reviews, or animal studies,
5. not related to AD or eczema,
6. not reporting data for patients 10 years or older, and
7. not evaluating the clinical, economic, or humanistic burden of AD (e.g., those investigating treatment efficacy).

3.2.4. Full text screening and data extraction

Full texts of studies deemed eligible based on title and abstract screening were downloaded and screened for inclusion. The following exclusion criteria were used for full text screening:

1. inaccessible study,
2. letters, editorial, case reports, non-systematic reviews, or animal studies,
3. not related to AD or eczema,
4. not reporting data for patients 10 years or older,
5. not evaluating the clinical, economic, or humanistic burden of AD (e.g., those investigating treatment efficacy), and
6. studies with experimental study designs (e.g., clinical trials).

Eligible studies from the full text screening phase were advanced to data extraction phase. Data were extracted in Microsoft Excel software. We searched the references of included studies to ensure no relevant studies were missed (known as snowballing). When potentially relevant studies were identified, they were screened and added to the data extraction pool if eligible. The PhD candidate (BE) was one of the team members screening full texts and extracting data from the eligible studies.

For each included study, we extracted any of the available data in four domains: clinical burden, economic burden, QoL scores, and humanistic burden other than QoL scores. The following general data were also extracted for each study: number of patients, age, male percent, and study design. We extracted the frequency of mentions for clinical symptoms related to signs, symptoms, and psychological factors, and the frequency of mentions for humanistic burden outcomes. We also extracted quantitative data for QoL scores, and economic burden of the disease. The psychological impact parameters were extracted under

both clinical and humanistic burden categories, as they were identified to influence both domains in the reviewed studies.

For each study, full text screening and data extraction were conducted by one reviewer, and it was revised for accuracy and completeness by another independent reviewer. If there were any conflicts, the senior researcher took the final decision.

3.2.5. Data adjustment and analysis

Disease severity terminologies and stages varied across studies leading to complicating assessment of severity (e.g. some studies grouped AD patients into 2 subgroups: mild and severe, or 3 subgroups: mild, moderate, and severe, or other more detailed subgroups reaching up to 5 severity levels). To address this, we standardized severities from different studies into an ordinal scale from 1 to 5, where rank 1 refers to mildest severity level. We created a map to match any type of severity level into our 5-level ordinal scale.

Data on economic burden of the disease were also reported in various formats across the included studies. Some studies reported data segmented by patient groups, specific populations, or timeframes (e.g., monthly, annually). The included studies also categorized costs heterogeneously into direct, indirect, medical, non-medial, or used other classifications. Additionally, studies reported costs in different currencies based on the study location, and in different years. We standardized and harmonized all the extracted data to ensure consistency as much as possible, creating a unified dataset to support comprehensive analysis. Details of data adjustment approaches conducted are shown in Supplementary Table S3.

QoL data were also heterogeneously reported. QoL was assessed using different questionnaires across the studies. For this, we transformed all QoL results into utility values ranging from 0 to 1. We mapped the results of all questionnaires into a unified 0-1 utility value through transforming all questionnaire results into EQ-5D index utility values through the available mapping tools (11, 65).

Loss in productivity costs were also adjusted and unified. All productivity loss values were transformed into number of days lost annually per patient due to the disease.

We created a multiple regression model to identify the main drivers of AD costs and reduction in QoL. We used IBM SPSS software (V25) to conduct the multiple regression analysis, applying a statistical significance level of 0.05. The dependent variables were AD costs and reduction in QoL, while the independent variables were severity rank, age, and gender. Several multiple regression models were constructed. We report only clinically and statistically significant models in the results. The PhD candidate (BE) conducted the analysis in collaboration with the research team members.

3.2.6. Risk of bias assessment

All studies included in the final data analysis were assessed for risk of bias using the Grading of Recommendations Assessment (GRADE) tool (66). Risk of bias assessment was conducted by one researcher and revised by another independent researcher for accuracy and completeness. If there were any conflicts, they were resolved through discussion between the two reviewers. The PhD candidate (BE) was one of the researchers' team conducting risk of bias assessment. A summary of the risk of bias assessment results is shown in Supplementary Figure S1.

3.3. Humanistic and economic burden of AD in the MEA region (Methods related to RQ2)

3.3.1. General overview of the aim, methodology and countries included

To further help decisionmakers in making evidence-informed decisions, country specific studies are needed. For this, we conducted a study to quantify the economic and humanistic burden of AD in adults and adolescents (≥ 10 years old) in the major countries in MEA. This region was selected as it has very diverse healthcare system structures and different levels of economic and social constraints. We did not include clinical burden in this study, as it was already reported in the global SLR, and we assumed the clinical effects of the disease will not differ significantly between countries, so we focused on humanistic and economic burden components. We included 7 countries from this region to be representative of the whole region. These include Saudi Arabia (KSA), Egypt, United Arab Emirates (UAE), Lebanon, South Africa, Kuwait, and Algeria.

The aim of the study was to estimate the economic and humanistic burden of AD in adults and adolescents in these countries. This was achieved through primary and secondary data collection from these countries to estimate the specific effect in each country, and to compare those countries. A literature search, and expert interviews were conducted to obtain and validate the values required to estimate burden of disease. A bottom-up approach was adopted based on the patient numbers and the average burden per patient in each country.

3.3.2. Estimating the number of patients

As a first step required for all further steps, we estimated the number of adult and adolescent AD patients in each of the seven countries included. We used prevalence data estimates from the GBD study (46). Table 1 below shows a summary of the estimated number of patients in each country in 2019. Supplementary Table S4 shows the detailed patient numbers by age group and gender.

Table 1 Estimated number of adult and adolescent AD patients in MEA countries in 2019

Country	Number of patients
Algeria	365,204
Egypt	545,217
Kuwait	41,691
Lebanon	44,161
KSA	342,885
South Africa	354,771
UAE	84,885

KSA: Kingdom of Saudi Arabia, UAE: United Arab Emirates

3.3.3. Humanistic burden

For humanistic burden estimations, we calculated the loss in QoL due to the disease in each country. This was based on multiplying the number of patients by the average utility lost per patient. Country-specific data was not available regarding the loss of QoL due to AD.

Therefore, we used international estimates for QoL values, and assumed that the differences in QoL per patient will not differ significantly from the global estimates.

Those estimates included a study by Beikert et al. (67) that estimated the QoL values for adult AD patients subgrouped by age. The study reported values as EQ-5D VAS values. We converted this data to utility values on a 0 to 1 scale to estimate the annual utility loss.

We also used estimates from another study (68) to estimate the QoL of AD adolescents (10-18 years). Ezzedine et al. reported QoL values using DLQI questionnaire. DLQI values were also converted to utility loss data to estimate loss in QoL using the 0 to 1 unified scale (68).

These studies provided data for QoL of patients with AD. For the burden of disease estimate, an estimate of utility loss due to AD was required. So these values were subtracted from the average population utility to estimate the difference, which represents the net effects of AD in QoL. Average population utility values were abstracted from a study by Janssen et al. (69).

Humanistic burden per country was estimated through two key measures. First, utility loss per country was calculated through multiplying the average utility loss per patient by the number of patients in each country. Second, we calculated a hypothetical estimate of the monetary values of QoL lost due to the disease to provide a broader societal perspective. This was estimated by multiplying each country's estimated annual QALYs lost by its gross domestic product (GDP) per capita. This calculation assumes that one lost QALY can be hypothetically valued at each country's GDP per capita for one year. This hypothetical estimate could help decisionmakers understand the burden from a societal perspective and compare it to other diseases.

To estimate the total utility loss per country, we created a table of average utility loss per AD patient, by age group, and multiplied the average utility loss per age group by the number of patients in each country by age group. The sum of these values in each countries provided the total QALYs lost by all patients due to AD in each country.

3.3.4. Direct healthcare costs

The economic burden of the disease included two distinct components: direct healthcare and indirect costs. Direct healthcare costs were represented in medical direct costs, which include topical treatments, outpatient visits, hospitalizations, systemic treatments, targeted therapy, and phototherapy sessions. All costs were reported in 2019 United States Dollars (USD).

We conducted structured expert interviews in each of the seven countries to estimate the costs and resource utilization for AD patients in each country. First, we created a draft questionnaire, and we validated this draft with an expert to ensure it captures all direct healthcare costs of the disease.

Next, we conducted a minimum of two local expert interviews in each country to fill in the questionnaire. We calculated the average of the two questionnaires results resembling the average direct medical costs. If, for any country, the results of the two expert questionnaires were significantly different, a third interview was conducted, and the results of the two lowest costs were used to be conservative. A significant difference between questionnaires was defined as double the value of the total cost. The experts were chosen based on convenience sampling. The Inclusion criteria were medical experts who have experience in dermatology and are currently treating AD patients in each country.

The questionnaire included the following domains: severity distribution (proportion of mild-moderate-severe patients), outpatient and inpatient visits, local and systemic treatments used, phototherapy sessions, targeted therapies, and other cost elements. Supplementary Table S5 shows the questionnaire used for estimating direct healthcare costs in all interviews.

After the interviews, we calculated the total annual direct cost of AD in each country, based on the questionnaire results and the number of patients in each country.

3.3.5. Indirect costs

Indirect costs were represented as productivity lost by AD patients due to absenteeism or presenteeism. To estimate the average number of days the patient is absent from work or school, or present but not productive, we conducted a targeted literature search including several studies reporting these values for AD patients. We calculated the average values for these studies to estimate the value of presenteeism and absenteeism. Because severity can be

a confounding factor for productivity loss estimated, we conducted the calculations through using a weighted average for severity, to correspond to the real severity distribution. Finally, we calculated the estimated number of days lost due to the disease.

The monetary value of the loss in productivity was calculated by multiplying the productivity loss per patient by the number of productive patients in each country and the average salary. We also adjusted the values to gender, unemployment rate, and the labor force participation rate (LFPR) to accurately estimate the productivity loss. The following equation was used for calculation of indirect costs in each country:

((LFPR (by gender) * (1- unemployment rate) * prevalence (by gender)) * (absenteeism + presenteeism in days) * Average daily salary

3.3.6. Validation

After estimating all values for humanistic burden, direct medical costs, and indirect costs, the data for each country were validated by experts from the country to check if the data matches what these experts expect for their countries. We conducted meetings with representatives of the seven countries with experts and payers for validation. The experts provided feedback on the results, validated some values sand asked for adjustments in other values to reflect the actual burden. During the validation meetings, experts were shown the detailed methodology and results, and they were asked if these results reflect their actual practice real life effects of the disease or not. They were also asked to recommend better data sources or better estimation approaches if available.

In this study, the PhD candidate (BE) participated in finding the relevant input sources for estimating the burden and conducting the experts' interviews. He also participated in compiling the data and creating the calculations to estimate the quantitative values. Additionally, he participated in the research term in analyzing the results and creating the final report and manuscript.

3.4. Hidden burden of AD in CEE countries (Methods related to RQ3)

3.4.1. General overview of the methodology

The results of the burden of disease in MEA study and the AD burden systematic review revealed that there is a significant hidden burden associated with AD, represented in its deteriorative effects on QoL and productivity losses for AD patients.

Therefore, our next study focused on the hidden burden of the disease. We defined the hidden disease burden as the combined impact of economic consequences due to productivity loss and QoL impairment caused by the disease.

In this study, we aimed to assess the size of this burden in adults and adolescents in CEE countries, to provide decisionmakers with results that could help them assess the real burden of the disease, after adding the traditional burden of disease components (e.g. treatment costs, effects on mortality and morbidity). CEE countries were defined as countries that are members of the European Union and are geographically located in CEE. These are 11 countries, and they include Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, and Slovenia.

The results in this study were reported in 2022 Euros. All costs and disease burden components were also adjusted to 2022 as it was the base year for this study.

3.4.2. Number of patients estimation

To estimate a quantitative value for any burden of disease component in a specific country using a bottom-up approach, we need to identify the number of affected patients in this country. For this, we abstracted prevalence data subgrouped by age group from the GBD study results (46). Table 2 below shows a summary of the estimated number of patients in 2022. Supplementary Table S6 shows the detailed estimated number of patients in each country by age group.

Table 2 Estimated number of adults adolescents with AD in CEE countries in 2022

Country	Number of patients
Poland	282,363
Hungary	109,718
Romania	101,527

Czechia	82,171
Bulgaria	50,513
Slovak Republic	42,643
Croatia	32,266
Estonia	25,173
Lithuania	22,397
Slovenia	16,225
Latvia	8,872

3.4.3. Humanistic burden

To estimate the humanistic burden due to AD, we subtracted the QoL values for AD patients from the general population's average QoL. The QoL values for AD patients were estimated using the methodology previously used in the MEA study, based on the two studies by Beikert et al. and Ezzedine et al. (67, 68).

For the general population QoL, we used a study reporting values for Poland as a representative for other CEE countries (70), due to the lack of similar studies in the other included countries, assuming that the QoL values will not differ significantly between these countries as they share similar socioeconomic status and cultural characteristics (71). A summary of the values extracted from the study is found in Supplementary Table S7.

For each patient age group, we calculated the average QoL loss due to AD, then we multiplied the resulting value with the number of patients in each subgroup to have a detailed table with QoL loss for each age group per country. Data were further adjusted to gender to eliminate the potential confounding due to gender differences.

The final equation to calculate the total humanistic burden per country was:

Σ ((General population utility for age group – utility of AD population in the age group) * Number of patients in the age group)

We also calculated the hypothetical estimated monetary value of QoL lost due to AD based on each country's GDP per capita assuming that one lost QALY hypothetically corresponds to each country's GDP per capita. Calculating this estimate was essential to show non-healthcare expert decisionmakers the size of burden due to loss in QoL.

3.4.4. Indirect costs

To calculate the indirect cost (represented in productivity loss), we used the same bottom-up approach, based on the number of patients per country and the average burden per patient. Productivity loss per patient estimate was calculated using the same methodology used in the MEA study productivity loss calculations. This is estimating the number of days lost due to absenteeism and presenteeism as a result of AD, then multiplying this value by the average daily salary and adjusting the final value to LFPR and unemployment rate per country.

3.4.5. Total hidden burden

Total hidden burden was a simple calculation summing the monetary value of QoL lost and productivity lost per country due to AD. This calculation resulted in an estimated monetary value showing a single value for each country for the hidden burden of the disease, which is very useful for decisionmakers in each country to make resource allocation decisions.

However, these values were not useful when comparing burden of disease between countries, as the countries differ in their population size, average salary and other characteristics, resulting in significant differences in the burden. To adjust for these and create a comparative figure showing the relation between the burden in these countries, we calculated a new value: the total hidden burden as a percentage of its GDP. This indicator shows a relative estimate of how much the disease affects the country and is comparable between various countries.

In this study, the PhD candidate (BE) searched for relevant input sources for estimating the burden. He also compiled the data and created the calculations to estimate the quantitative values. Additionally, he analyzed the results and created the final report and manuscript in collaboration with the co-authors.

3.5. **Reducing the burden of AD (Methods related to RQ4)**

The aim of this study was to propose policy actions to be implemented by decision makers to reduce the disease burden and complement the quantified values with strategies. However, a specific policy intervention might be relevant for a country but not suitable to another. Therefore, we conducted a study including experts from several countries to show different perspectives and provide a list of potential interventions. Decision makers in each country can use the results of this study to tailor specific action plans based on their local settings.

As a first step, we conducted a global scoping review to identify potential interventions or recommendations that have been proposed to reduce the burden of AD. This review was the foundation for the subsequent expert engagement activities. Next, two rounds of expert panel meetings were organized, with an interim survey conducted between the rounds to inform and guide the discussions. In the first round, an expert panel of healthcare decisionmakers was convened to discuss the scoping review findings. Following this, a structured survey was administered to the same experts to collect their opinions on the primary list of potential interventions. Based on the survey results, a second round of the expert panel discussions was held to validate the findings, identify the most potential actions, and show the pros and cons of each intervention. Finally, we formulated all findings into specific actions and grouped these into five domains. These domains included capacity building, research, guidelines, patient support and education, and public awareness.

3.5.1. Scoping literature review

The scoping literature review was conducted in September 2021. We included studies that discussed actions or recommendations by policymakers to reduce any AD burden of disease component (economic burden, clinical burden, or humanistic burden). We searched PubMed for peer-reviewed studies and Google Search engine for reports or white papers. The actions were grouped into 6 domains according to their aim. The search terms used for the scoping review were based on 2 domains: atopic dermatitis and policy actions. The search strategy was designed to identify key policy actions to reduce the burden of AD, rather than to comprehensively capture all possible interventions. Therefore, we intentionally focused on specific terms commonly used in policy and health system contexts, rather than broader terms

such as “interventions” and “actions”, which could have diluted the specificity of our search. This targeted approach ensured we focussed on the relevant actions that can serve as a foundation for expert discussions in subsequent steps. The search term used for searching potential policy interventions is shown in Supplementary Table S8.

3.5.2. Expert panel

We convened an expert panel comprising seven healthcare policymakers from seven countries across the MEA region to ensure a diverse and comprehensive perspective on potential interventions. In addition, an international health policy expert moderated the expert panel. They discussed each identified intervention from the scoping review based on its applicability and potential impact in an open discussion. To be included in the expert panel, an expert had to be a high-level health policy decisionmaker in his/ her country, and to have relevant experience with burden of disease and resource allocation concepts.

3.5.3. Expert survey

For a more structured approach to evaluating potential interventions, we created an online survey and shared it with the seven experts. They were asked to rank the six action domains by prominence, then to identify the most promising recommendations within each domain.

3.5.4. Validation expert panel and formulating the recommendations

Following the survey, the experts reviewed and validated the survey results in the second expert panel, with the moderation of the international policy expert. The panel aimed to create a comprehensive list on all aspects related to the potential actions. The experts discussed each potential action, and had a crystallized picture of the most potential recommendations before reaching consensus on the list. The panel members also agreed to merge two of the original domains and kept only five action domains. Finally, a full list of potential interventions was created and formulated with details, and it was revised and validated by the experts.

In this study, the PhD candidate (BE) participated in the scoping literature review, analyzed the interviews, helped in formulating the final recommendations, and co-authored the final report and manuscript.

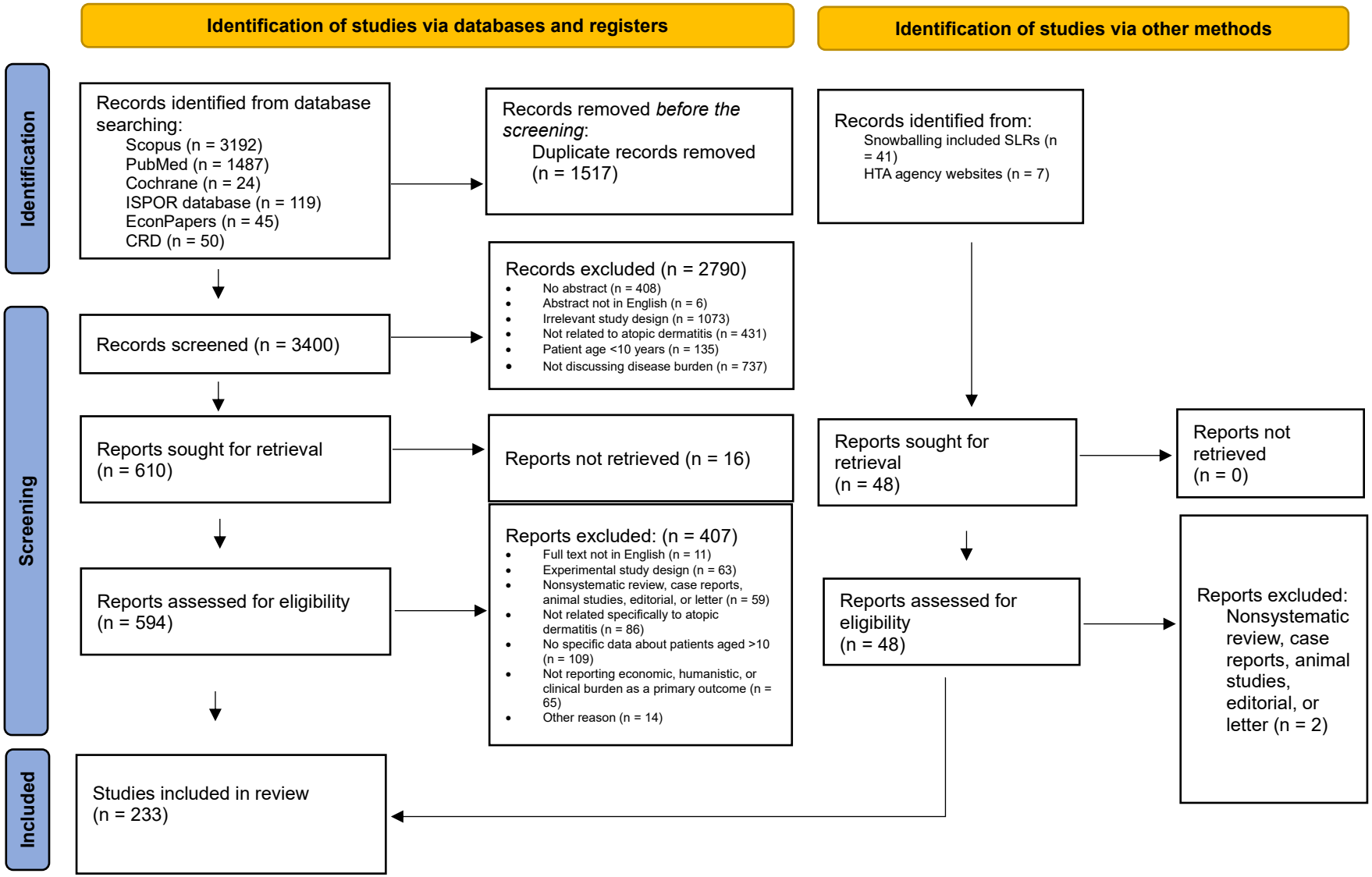

Figure 2 Systematic literature review PRISMA diagram

4. Results

4.1. **Systematic literature review on the burden of AD (Findings related to RQ1)**

4.1.1. General results

The systematic search resulted in 3,400 records after removing duplicates from various databases. Additionally, 48 additional studies were identified through other methods. After double screening titles and abstracts these records, 610 studies were deemed relevant for full text screening. Full text screening phase excluded 407 records from search databases, 2 studies from other sources, and 16 records were inaccessible. Finally, 233 records were eligible for final inclusion and analysis. Figure 2 shows the PRISMA flow diagram (64).

4.1.2. Included studies' characteristics

Most of the included studies (66%) provided AD burden details from Europe and Central Asia, though the United States was the most common country of the included studies (46 records), followed by Germany (35 records). There was only one study reporting data from a low-income country, while most of the studies included focused on high income countries (85%). Observational studies were the majority of the included studies (90%), while only nine studies were economic models, and 36 studies were systematic reviews.

4.1.3. Clinical burden

Itch, depression, and anxiety were by far the most commonly reported impact parameters related to the clinical burden of AD. Other clinical burden outcomes were also mentioned in some studies including soreness, skin dryness (also known as xerosis), redness (also knows as erythema), and suicidal ideas.

Subgroup	Impact	Frequency of mentions, n
Psychological	Depression	49
	Anxiety	42
	Suicidal ideation	11
	Stress	9
	Other psychological impacts	8
Signs	Itch or pruritis	51
	Soreness/pain/tenderness	20
	Burning or heat or tingling sensation	6
	Skin tightness	2
	Skin sensitivity/sensitivity to sun	1
Symptoms	Dryness (xerosis)	13
	Redness (erythema)	11
	Bumps/blisters/papules/vesicles	6
	Thickening/lichenification	6
	Cracking/fissuring	5
	Edema/swelling	4
	Scaling/peeling	3
	Hardening/flaking	2
	Bleeding	2

Figure 3 Frequency of mentioning different clinical burden effects of AD in the included studies

Figure 3 shows the frequency of mentions of each of the clinical burden outcome sin the included studies, subgrouped by psychological impacts, signs, and symptoms. .

Itch had a very high prevalence among AD patients in the included studies, with values reaching up to 100% of patients in some studies. However, some studies also reported low levels of itch among AD patients as low as 21% (72-77).

Several included studies asked patients about the level of itch they feel using the Peak Pruritus Numerical Rating Scale (NRS-itch) (78) and asked them to provide a score for this

level on a 0 to 10 scale, where 10 represents the worst itch feeling. Studies either reported the mean or median itch levels among patients. In both types of studies, the average reported level of itch was 6 (range 4-9 for median, and 3-9 for mean).

For depression, several studies provided quantitative values for prevalence of depression among AD patients, as diagnosed by an expert. According to the included studies, the average depression prevalence among AD patients was 18% (Range 3%-57%). However, for patients'-reported depression, the average was even higher with 26% prevalence (range 10% to 37%).

For anxiety, prevalence had similarly high values, with an average of 24% (Range 1%-64%). One study reported that 41% of AD patients had moderate or severe anxiety, as they scored 11 points or more in the Hospital Anxiety and Depression Score (HADS) (79). HADS is one of the most popular anxiety questionnaires providing scores ranging from 0 to 21. Patients with mild symptoms score between 8 and 10, while those with severe symptoms score 11 or higher (80, 81).

4.1.4. Humanistic burden

Humanistic burden is reported based on two outcomes: the frequency of mentions of humanistic burden components, and the QoL scores of AD patients. AD reduces the QoL of patients through several mechanisms. Psychological impacts were clearly the most mentioned mechanism to reduce AD patients' QoL with 78 mentions among the included studies.

Impact	Frequency of mentions, n
Psychological	78
Sleep disturbance	55
Limitation in daily activity	33
Limitation in role: work	29
Limitation in social/leisure activities	25
Problems with interpersonal relationships	22
Limitation in role: school	21
Physical limitation	19
Problems with sexual functioning	15
Scratching	13
Bodily/physical discomfort	11
Lack of concentration	4
Suboptimal skin-related health perceptions/cognitions	4
Financial burden of buying special products	2

Figure 4 Frequency of mentioning humanistic burden impacts in the included studies

Additionally, other factors like sleep disturbance and limitations in daily activities also significantly affected patients' QoL. This was clear for the frequency of mentions of these impacts in the included studies. Figure 4 shows the frequency of mentions of each of these, in addition to several other mechanisms responsible for reducing AD patients' QoLs with their frequency of mentions.

Sleep disturbance especially had special focus among the included studies with some studies reporting up to 70% of AD patients suffering from any form of sleep disturbance, such as difficulty in sleep induction or nocturnal awakening due to itch. Girolomoni et al. (82) presented detailed subgroups of AD patients according to sleep disturbances, and showed that more than 50% of patients had mild-moderate sleep difficulties, and approximately 10% have severe sleep disturbance difficulties due to AD. Eckert et al. (83) reported that adequate AD control can reduce sleep disturbances prevalence from 24% to 9%, emphasizing the role of controlling the disease effectively on QoL.

Several questionnaires were used to assess AD patients' QoL, including DLQI, Visual Analog Scale (VAS), 36-Item Short Form Health Survey (36-HF), Patient-Oriented Eczema Measure (POEM), EQ-5D, AD Burden Scale, and Skindex. Most of these questionnaires provided data subgrouped by several levels of severity, since the QoL of a mild AD patient is significantly different than that of a severe patient.

Our systematic review included 597 data points reporting QoL questionnaires results for AD patients. These data were adjusted and aggregated to create Table 3 below, which shows the average utility value for each severity in addition to an average utility value for the unstratified population for data points reporting AD patients QoL without severity subgroups.

Table 3 AD patient's QoL average utility values based on the included studies

Severity rank	**Number of studies reporting values**	**Average utility**	**Minimum utility**	**Maximum utility**
Unstratified population	71	**0.779**	0.432	0.940
1	3	**0.873**	0.869	0.877
2	25	**0.807**	0.732	0.912
3	15	**0.728**	0.633	0.832
4	25	**0.676**	0.551	0.881
5	3	**0.548**	0.420	0.668

Among the two dependent variables assessed in the multivariate regression model, only QoL was significantly affected by the independent variables. AD costs were not significantly affected by severity age, or gender based on the results of the included studies. Ad for QoL, the multiple regression model showed that male AD patients had a significantly lower QoL versus female AD patients (β = -0.863, p = 0.002). It also showed that age was not a significant factor for reduced QoL (β = -0.005, p = 0.105). Higher disease severity levels were inversely associated with QoL. For instance, compared to severity rank 4 (reference category), severity rank 2 was associated with a significant positive effect on QoL (β = 0.108,

$p < 0.001$), while severity rank 3 shows a smaller, non-significant positive association ($\beta = 0.086$, $p = 0.087$). Supplementary Table S9 shows the details of the QoL regression model.

4.1.5. Economic burden

The included studies discussed economic burden of AD as direct and indirect costs. Some studies reported the total direct cost as a lump sum, while others provided a detailed breakdown of resource utilization contributing to these costs.

Concerning healthcare resource utilization, Studies that did not subgroup patients by severity showed that on average, AD patients visit dermatologists 8.6 times annually on average (range 2.8 to 16.3), while primary care/ general practitioner visits averaged 16.5 visits annually (range 5.3 to 32.8).

Emergency visits and hospitalizations were not common among AD patients in all severity levels. For studies reporting resource utilization values by severity, as severity increased, the frequency of emergency visits and hospitalization increased. For studies reporting data for general AD patients, emergency visits frequency was low at an average of 0.8 emergency visits annually (range 0.05-1.22). Hospitalizations average annual frequency was also low, with 0.45 (range 0.08-1.46), and 0.75 (range 0.00-1.16) annual hospitalizations for severity ranks 2 and 4, respectively.

Total costs were difficult to compare among studies, due to difference in each study's country, patient severity levels, treatment guidelines, income levels, and inclusion of cost components. We calculated an average among all studies reporting total cost, and the average was 5,246 USD (2020) annually per patient (range 769 to 23,638 USD). Total direct costs were 4,411 USD on average, and total indirect costs were 9,068 USD on average. Table 4 below shows a summary of direct and indirect cost average values form the included studies.

Table 4 Average annual cost per AD patient

Type of economic burden	Number of studies reporting the cost	Number of patients in the studies	Minimum reported cost/ USD	Average cost/ USD	Maximum reported cost/ USD
Total direct cost	9	119,750	940	**4411**	11,536
Total indirect cost	3	218	1289	**9068**	15,650

Costs are in 2020 USD

For indirect costs, several studies reported absenteeism and presenteeism values to report productivity loss due to AD. Twenty studies reported absenteeism values, 13 studies reported presenteeism values, and 14 studies reported both absenteeism and presenteeism values due to AD.

Annually, AD patients lose 68.8 days of productivity on average due to their disease, including both absenteeism (14.8 days) and presenteeism (54.0 days). Table 5 below shows a summary of the calculated average productivity loss values due to AD, showing an increasing trend in the number of days lost as severity increases.

Table 5 Productivity loss average values due to AD

Severity rank	Absenteeism only (days)	Presenteeism only (days)	Total (days)
Unstratified population	14.8	54.0	68.8
1	2.5	13.6	16.1
2	14.0	58.5	72.5
3	23.3	78.5	101.8
4	24.0	95.5	119.4
5	26.5	92.5	119.0

4.2. Humanistic and economic burden of AD in the MEA region (Findings related to RQ2)

4.2.1. Humanistic burden

We calculated the average utility loss per patient in each age group. Table 6 below shows summarizes the data abstracted from the literature about the general population utility and the utility of average severity AD patients by age groups. It also shows the difference between those values, assumed to be the annual utility loss per patient due to AD in each age group.

Table 6 Annual utility loss per patient due to AD

Age range, years	Average non-patient utility*	Average AD patient utility†	Average utility lost per AD patient
10–14	0.93	0.76	0.17
15–19	0.93	0.70	0.23
20–24	0.93	0.77	0.15
25–34	0.92	0.73	0.18
35–44	0.90	0.71	0.19
45–54	0.86	0.68	0.18
55–64	0.82	0.54	0.28
65–74	0.80	0.71	0.09
≥75	0.72	0.61	0.11

* Adapted from Janssen et al. (69)

†Adapted from Beikert et al. (67) and Ezzedine et al. (68)

The results show that utility losses due to AD vary by age with no clear trend. Average utility losses due to AD range from 0.09 to 0.28 for the various age groups, with the group of 55-64 suffering the highest annual utility loss, and the group aged 65-74 suffering the least utility losses due to the disease.

Table 7 below shows the annual QALY loss due to AD across the age groups and countries included. Because AD is a non-fatal disease, annual utility loss was assumed to be equal to

annual QALY losses. Due to the absent or negligible effect of AD on survival (the other component of QALYs).

Table 7 Annual QALY loss per country due to AD

Age range	Utility Loss for AD per patient	QALY loss per year						
		Egypt	Algeria	South Africa	Saudi Arabia	United Arab Emirates	Lebanon	Kuwait
10-14	0.17	18,337	9,893	15,548	6,724	1,122	1,152	761
15-19	0.23	17,381	9,204	13,464	7,841	1,037	1,028	710
20-24	0.15	11,104	6,510	6,598	6,446	638	707	599
25-34	0.18	22,984	17,116	11,545	18,438	4,139	2,215	2,313
35-44	0.19	16,420	13,109	7,326	15,414	6,374	1,515	2,091
45-54	0.18	8,150	6,738	4,856	6,006	2,041	838	889
55-64	0.28	6,583	5,052	5,843	2,953	670	683	414
65-74	0.09	874	716	1,102	286	38	119	38
Above 75	0.11	405	452	689	108	7	96	25
Sum		**102,238**	**68,789**	**66,972**	**64,215**	**16,067**	**8,352**	**7,840**

Annual QALY losses differed significantly between different countries ranging from 7,840 QALYs lost annually in Kuwait, to 102,238 QALYs lost in Egypt. The results should be interpreted carefully, as the QALY loss calculation includes several confounding factors such as population size and age distribution pattern.

Because each country differs in the age distribution structure and number of AD patients, the average AD loss per patient per country was not similar. We calculated the weighted average utility loss per patient for each country, to show on average how much utilities are lost per patient in each country. However, the values were very close, ranging from 0.185 in Lebanon to 0.189 in United Arab Emirates, showing that approximately, an AD patient loses 20% of his/her annual QoL due to the disease.

4.2.2. Economic burden

4.2.2.1. Direct healthcare costs

Expert interviews and data from the literature provided estimations for the average direct healthcare costs per AD patient per year. Total AD healthcare costs per country involve the number of patients in each country as well. Table 8 shows a summary of average annual cost per patient and the total annal cost per country. All provided values in the table are in 2019 United States Dollars (USD).

Table 8 AD Healthcare costs (direct costs) per country

Country	Average annual cost per patient/USD	Annual cost per country/million USD
Algeria	312	42.8
Egypt	469	95.5
Kuwait	2,880	44.8
Lebanon	817	13.6
Saudi Arabia	780	99.5
South Africa	449	60.1
United Arab Emirates	3,569	112.5

Costs are in 2019 USD

The annual treatment costs for an AD patient vary widely in the selected countries, ranging from 312 USD in Algeria, up to 3,569 USD in United Arab Emirates. Similarly, the annual treatment cost per country shows significant variation, range from 13.6 million USD in Lebanon up to 112.5 million USD in United Arba Emirates. However, direct comparisons of annual treatment costs across countries should not be performed, as the number of patients differ significantly between countries, influencing the overall expenditure.

4.2.2.2. Indirect costs (productivity losses)

Based on the simple literature research we conducted, the average productivity loss for an AD patient was approximately 6.1 days annually due to absenteeism, and 22.9 days due to presenteeism, summing up to 28.9 days of productivity lost annually due to the disease.

Country specific productivity losses showed a wide range of assumed economic losses due to AD patients' absenteeism and presenteeism. Table 9 below summarizes the indirect costs per country in 2019 USD and shows a calculation of the value of indirect costs as a percentage of each country's GDP to allow for cross country comparison. Indirect costs as a percentage of GDP ranged from 0.022% in Algeria to 0.061% in Lebanon.

Table 9 Indirect costs due to AD per country

Country	Indirect costs / million USD	Indirect costs as a % of GDP
Algeria	37.9	0.022%
Egypt	54.9	0.022%
Saudi Arabia	363.7	0.046%
Kuwait	61.8	0.044%
Lebanon	33.3	0.061%
South Africa	152.1	0.041%
United Arab Emirates	228.0	0.054%

Costs are in 2019 USD

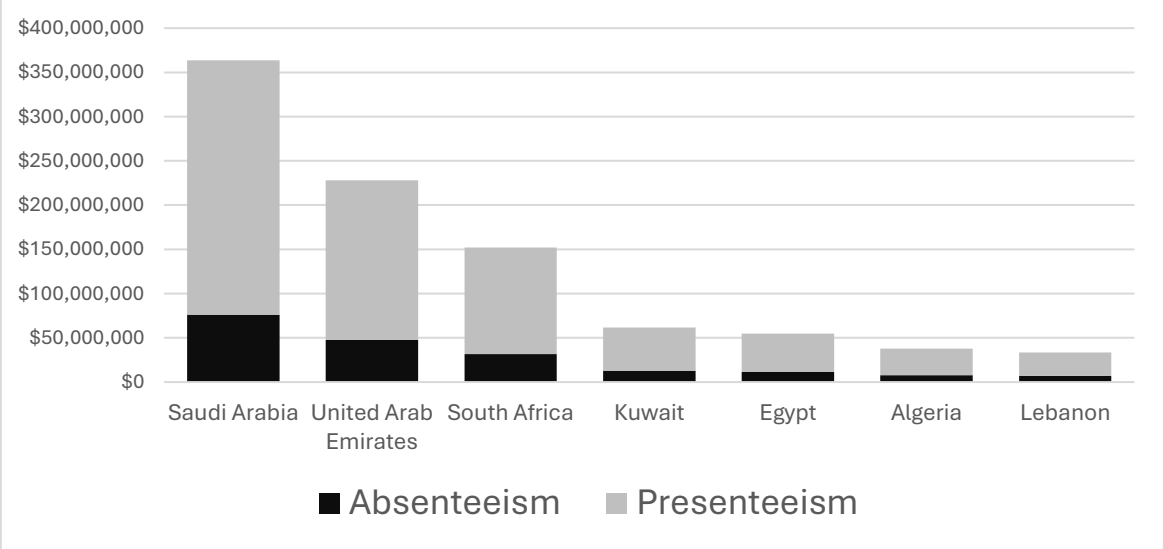

Figure 5 Total indirect costs in countries subgrouped by direct and indirect costs

Figure *5* shows a summary of indirect costs per country, subgrouped by absenteeism and presenteeism components.

4.2.3. Total burden

The total burden component including direct costs, indirect costs, and monetary value of QALYs lost are presented in Table 10 below. All costs in the table are in million 2019 USD. The total annal burden of AD in the selected countries range from 113.9 million USD in Lebanon to 1,961.8 million USD in Saudi Arabia.

Table 10 AD total burden including economic burden and humanistic burden

Country	**Economic burden**			**Monetary Value of QALYs lost */** million USD	**Total burden*/** million USD
	Healthcare costs*/ million USD	**Indirect costs**/ million USD**	**Total economic burden†*/ million USD**		
Algeria	42.8 (53%)	37.9 (47%)	80.7	285.7	366.4
Egypt	95.5 (63%)	54.9 (37%)	150.4	259.4	409.8

Kuwait	44.8 (42%)	61.7 (58%)	106.5	266.5	373.0
Lebanon	13.6 (29%)	33.3 (71%)	46.9	66.9	113.9
Saudi Arabia	99.5 (21%)	363.7 (79%)	463.2	1,498.6	1,961.8
South Africa	60.1 (28%)	152.1 (72%)	212.2	426.8	639.0
United Arab Emirates	112.5 (33%)	228.0 (67%)	340.5	704.4	1,044.9

All costs are shown in million 2019 USD

*million USD (% of total economic burden)

†The sum of healthcare costs and indirect costs/ million USD

However, all these values are not comparable between countries. For this, I created Table 11, to allow comparability between countries, as the values are adjusted to the national GDP of each country. Values in the table are in proportions of the GDP per country. The results show that AD consumes a significant value of the GDP for a non-fatal skin disease. It consumed values ranging from 0.164% of the national GDP (Egypt), up to 0.265% of the national GDP (Kuwait).

Table 11 AD burden components as a percentage of national GDP per country

	Cost as % of GDP				
Country	**Economic burden**			**Monetary Value of QALYs lost**	**Total burden**
	Healthcare cost	**Indirect cost**	**Total economic burden†**		
Algeria	0.022	0.024	0.046	0.163	0.209
Egypt	0.038	0.022	0.060	0.104	0.164

Kuwait	0.032	0.044	0.076	0.189	0.265
Lebanon	0.025	0.061	0.085	0.122	0.207
Saudi Arabia	0.013	0.046	0.059	0.191	0.249
South Africa	0.016	0.041	0.058	0.116	0.174
United Arab Emirates	0.027	0.054	0.081	0.167	0.247

†The sum of healthcare costs and indirect costs

4.3. **Hidden burden of AD in CEE countries (Findings related to RQ3)**

4.3.1. Humanistic burden

Similar to the humanistic burden estimated for the MEA region study, we estimated the QoL loss in CEE countries. Table 12 below shows the annual estimates QALYs lost due to AD per country, subgrouped by age groups. The table also provides an estimate of the total QALYs lost in each country. These ranged from 1,832 QALYs in Latvia to 58,856 QALYs in Poland. The weighted average utility loss values were close, having a narrow range from 0.205-0.209 among CEE countries.

Additionally, Table 12 shows the estimated monetary values of QALYs lost due to AD ranging from 38 million Euros annually in Latvia, to more than 1 billion Euros annually in Poland.

The values shown in Table 12 do not allow for cross country comparability, because the CEE countries differ in their population sizes, GDPs and age group distributions.

Table 12 Annual humanistic burden due to AD

Age range	Poland	Hungary	Romania	Czechia	Bulgaria	Slovakia	Croatia	Estonia	Lithuania	Slovenia	Latvia
QALYs lost in 10-14 range	8,404	3,337	3,564	2,664	1,489	1,309	964	1,001	709	475	347
QALYs lost in 15-19 range	6,879	2,882	2,696	1,894	1,184	1,067	816	676	589	377	228
QALYs lost in 20-24 range	3,779	1,497	1,218	911	550	580	462	306	310	194	95
QALYs lost in 25-34 range	7,868	2,670	2,247	2,031	1,226	1,198	768	667	555	384	210
QALYs lost in 35-44 range	8,312	3,197	2,526	2,348	1,335	1,267	798	608	476	440	177
QALYs lost in 45-54 range	6,345	2,702	2,620	2,081	1,284	1,027	778	550	557	419	196
QALYs lost in 55-64 range	11,182	3,875	3,751	2,916	1,996	1,638	1,312	870	933	672	361
QALYs lost in 65-74 range	3,415	1,319	1,253	1,111	720	485	394	252	243	196	106
QALYs lost in above 75 range	2,672	1,179	1,085	890	597	352	388	281	287	205	113
Total QALYS lost (per population)	**58,856**	**22,656**	**20,960**	**16,846**	**10,382**	**8,922**	**6,680**	**5,210**	**4,658**	**3,363**	**1,832**
Weighted Average Utility Loss (per patient)	0.208	0.206	0.206	0.205	0.206	0.209	0.207	0.207	0.208	0.207	0.207
Monetary value of QALYs lost/ million EUR	**1,024**	**397**	**316**	**442**	**136**	**180**	**117**	**140**	**110**	**94**	**38**

EUR: Euros, QALYs: Quality-adjusted Life Years

4.3.2. Indirect costs (productivity losses)

For productivity loss calculations, we present the indirect cost details in Table 13 below. Presenteeism represent the larger proportion of productivity loss due to AD. Estimated total indirect costs ranged from 3.6 million EUR in Latvia, up to 149 million EUR in Poland. However, these values are not comparable, due to the different settings among countries.

Table 13 Indirect costs of AD in CEE countries

Country	Indirect costs (absenteeism)/EUR	Indirect costs (presenteeism)/EUR	Total indirect cost/EUR
Poland	31,131,114	117,750,982	148,882,096
Hungary	9,601,467	36,316,792	45,918,259
Romania	5,644,941	21,351,545	26,996,486
Czechia	11,661,309	44,107,982	55,769,291
Bulgaria	3,433,068	12,985,310	16,418,378
Slovakia	4,065,516	15,377,494	19,443,010
Croatia	2,752,817	10,412,312	13,165,129
Estonia	3,384,810	12,802,775	16,187,585
Lithuania	2,452,073	9,274,773	11,726,846
Slovenia	1,962,584	7,423,318	9,385,902
Latvia	747,295	2,826,586	3,573,881

4.3.3. Total hidden burden

The total hidden burden for AD in CEE countries showed a significantly larger components of QALYs lost compared to productivity losses. The total burden ranged from 42 million EUR annually in Latvia, to 1.2 billion EUR in Poland.

Table 14 Total AD hidden burden in CEE countries

Country	Monetary value of QALYs lost/EUR	Indirect costs/EUR	Total hidden costs/EUR
Poland	1,023,992,982	148,882,096	1,172,875,078
Hungary	397,238,250	45,918,259	443,156,509
Romania	316,320,614	26,996,486	343,317,100
Czechia	442,137,697	55,769,291	497,906,987
Bulgaria	135,779,348	16,418,378	152,197,725
Slovakia	180,108,395	19,443,010	199,551,404
Croatia	116,799,725	13,165,129	129,964,853
Estonia	140,182,768	16,187,585	156,370,353
Lithuania	109,810,527	11,726,846	121,537,373
Slovenia	94,072,208	9,385,902	103,458,110
Latvia	38,019,556	3,573,881	41,593,436

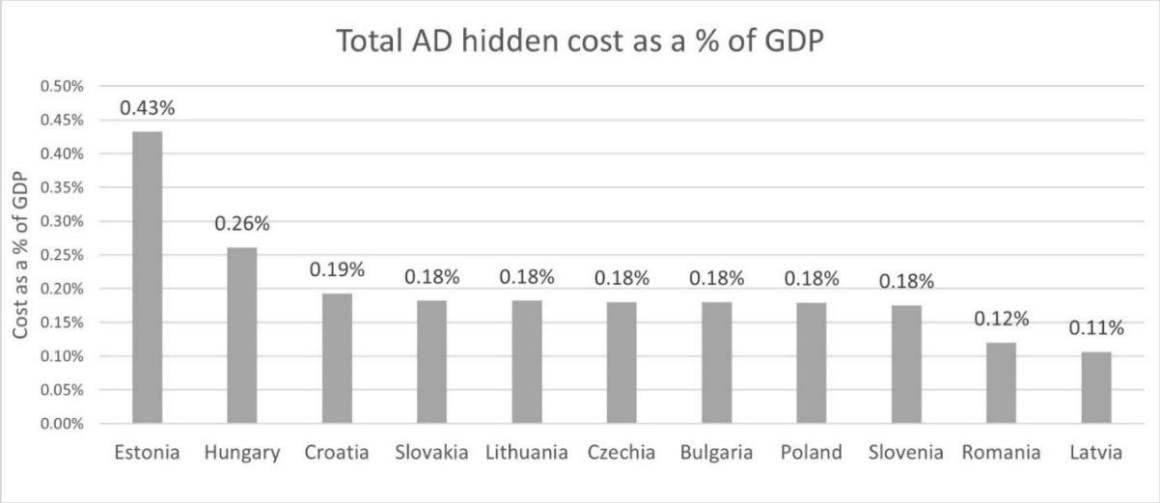

Figure 6 Total AD hidden burden as a percentage of GDP in CEE countries

To allow comparability between these countries and understand the relative effect of AD hidden burden on each country, we created Figure 6 above. This figure compares the total

AD hidden burden values (presented in Table 14) as a percentage of the national GDP of each country. This allows cross country comparison and shows that Estonia was the most affected by AD with the disease consuming 0.43% of its GDP for its hidden burden components only, and that Latvia was the least affected with the hidden burden of AD consuming 0.11% of its GDP.

4.4. **Reducing the burden of AD (Findings related to RQ4)**

4.4.1. Scoping review

For the reduction of AD burden study, we identified 397 hits from the search, of which 83 were eligible for inclusion and data analysis as they included relevant data about potential actions for reducing the burden of AD. The actions identified were categorized into six action domains: capacity building, public awareness, patient education, patient support, guidelines, and research. All actions extracted from the literature were grouped into these domains as shown in Table 15 below.

Table 15 Potential actions identified from the literature categorized into six action domains

Domain	Detailed actions
Research related actions	• Quantify the burden of AD on patients and caregivers • Conduct research to assess the loss in QoL due to the disease • Develop a national action plan to reduce AD burden • Study the impact of nurse-led clinics • Study the effect of communication on steroid phobia • Research to identify the gaps in the diagnosis and treatment of AD • Research to enhance patient adherence to medications and special formulations • Conduct research to identify the most impactful communication methods

Capacity building related actions	• Increase the number of dermatologists • Specialized training/education for nurses and general practitioners (GPs) in dermatology • Communication skills training for dermatologists • Develop telemedicine to compensate for the low number and uneven distribution of dermatologists among geographical regions • Provide consultation fees to physicians from public resources for patient education
Guidelines related actions	• Using unified and validated measures of AD severity by all stakeholders in the health system • Define specific evidence-informed guidelines for treatments • Involve nurses in patient education as they may have more time to spend with patients than dermatologists (this would provide better outcomes) • Establish recommendations for multidisciplinary care concept where the medical team should include dermatologists, pediatricians, nutritionists, and psychologists. • Develop guidelines for hospitalization of treatment-resistant patients • Monitor and evaluate quality of care with relevant and practical metrics • Encourage shared decision-making with patients to improve their adherence (e.g., involving patients in the choice of moisturizers) • Prescribe an adequate amount of moisturizers (not more and not less) • Include psychological therapy to the treatment protocol • Individualize patient treatment and care based on specific needs and characteristics of each patient (disease severity, age, educational level, etc.)

	• Update therapeutic plan in scheduled follow-up visits • Monitor and improve patients' adherence
Patient education related actions	***1. Content of patient education*** • Application of topical interventions in an effective way • Allergens that increase the severity and frequency of flares • Benefits and safety of topical corticosteroids to reduce steroid phobia • Avoidance of certain detergents and dealing with laundry • Management of symptoms (e.g., itch) ***2. Channels of patient education*** • Involvement of different health care professionals (dermatologists, GPs and nurses) to patient education • Explanation by health care professionals how topical medications should be applied • Printed materials (e.g., written plan on disease management) • Other educational channels like posters, videos (doctor-patient interviews), widgets, reminders, booklets, and drawings of objects of everyday life ***3. General guidelines for education*** • Educating parents and caregivers in addition to patients • Frequency of follow-up visits with patients • Advice for using online search (what to search and the validity of the information) • Management of the training programs (face to face meetings/ online content/ how many hours should be invested/ group education/educating patients by age groups) • Offering (but not forcing) patient education about management of AD

Patient support related actions	**1. Support domains** • Provide psychological and emotional support • Provide behavioral support • Improve adherence by detailed communication with patients **2. Patient support channels:** • Patient support and patient advocacy groups • Support groups for parents of children with AD • School support programs • Online support programs • Setting up patient organizations and empowering existing patient organizations • Provide financial support to AD patients to reduce the burden on households
Public awareness related actions	• Educate the public about AD to reduce the social stigma and help patients feel more accepted by their peers • Promote smoking cessation to decrease the prevalence of the disease • Encourage the use of powder-free gloves to reduce the incidence of AD • Share a consistent message through different channels across countries and regions

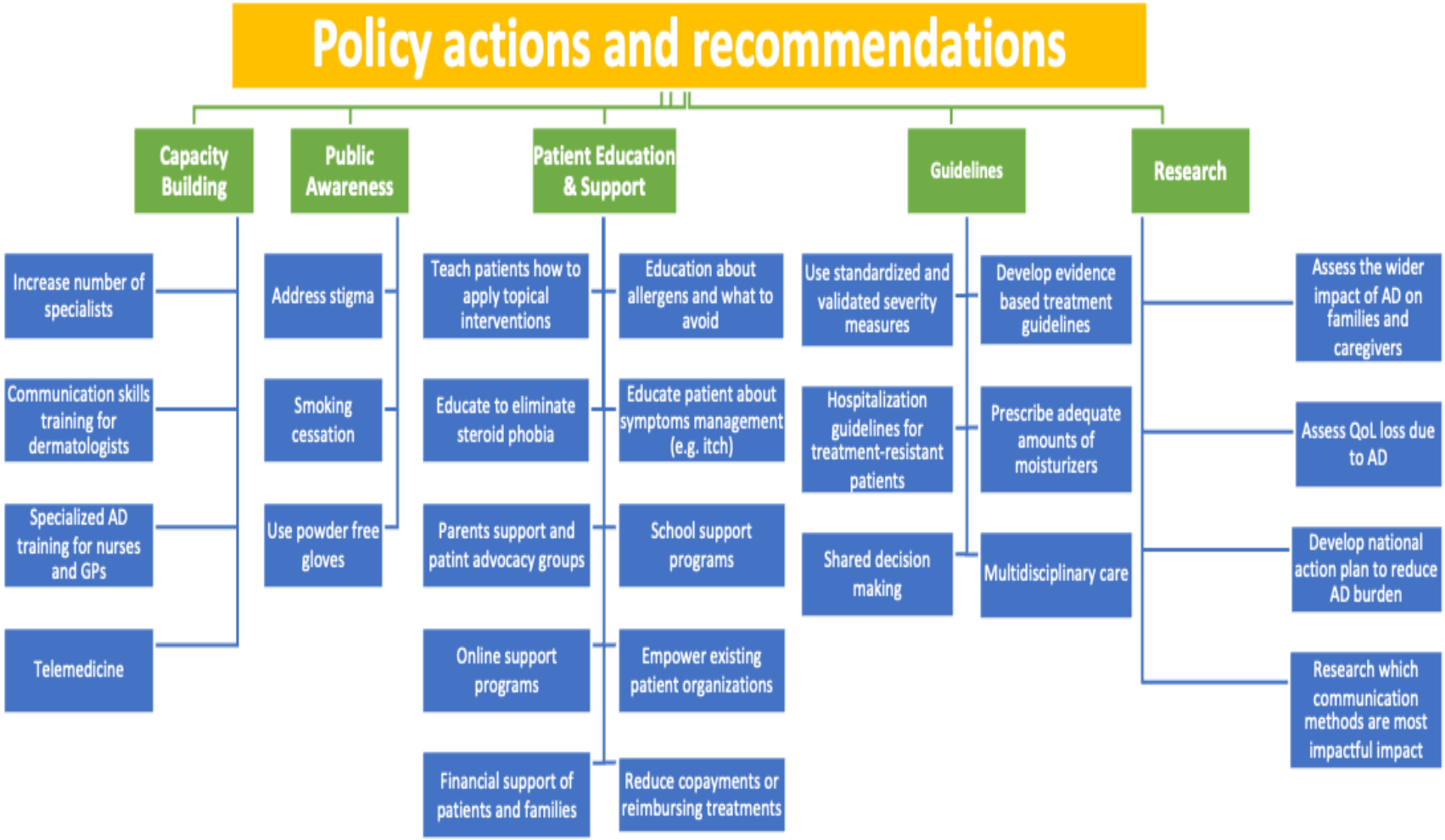

Figure 7 Summary of potential actions and recommendations to reduce the burden of AD

4.4.3. Expert panels and survey

During the expert meetings, they agreed to merge two of the action domains: “patient support” and “patient education”, as there was consensus that these domains are closely related, and that some actions can fit in both domains.

The experts’ panels and survey helped experts to formulate the uncategorized, and unharmonized action domains into clear and specific actions, and they prioritized those actions that might have a higher impact on reducing the burden. A summary of the general policy actions and recommendations was created and validated during these meetings. This is presented in Figure 7. It shows the five action domains with detailed actions. Some of these actions were relevant to certain settings, and others were relevant to all settings. The figure shows all recommended actions without details of relevance to each specific setting.

Capacity-building actions prioritize increasing the number of specialists and providing specialized training for healthcare professionals, including dermatologists, nurses, and general practitioners. Additionally, telemedicine was highlighted as an important tool to expand access to care.

Public awareness domain initiatives focus on addressing social stigma, promoting smoking cessation, and encouraging the use of preventive measures like powder-free gloves.

Developing evidence-informed treatment guidelines, using standardized severity measures, and ensuring the availability of essential treatments like moisturizers, form the foundation of guideline-focused actions.

Lastly, research domain priorities include assessing the broader impact of AD on families, understanding the QoL burden, and devising national action plans to reduce AD prevalence effectively.

4.4.4. Final recommendations

After the experts’ panels, and survey, the experts created a simple concise list with the most potential actions based on the ease of implementation and highest impact. This list was created through collaborative discussions between the experts after comparing the various

options' perceived potential to reduce the burden. Below, we present the distilled shortlist recommendations and policy actions suggested to reduce the burden of AD based on expert consensus:

- Create country-specific action plans for policy interventions that should target different stakeholder groups.
- Improve patient access to more effective medicines to provide an opportunity to reduce the burden of AD.
- The relevant group of healthcare professionals (dermatologists, general practitioners, pharmacists, nurses) should be selected to provide patient education in each country.
- Empower social media for public awareness about AD and its management.
- Conduct cost-effectiveness studies with a broader societal perspective (including indirect costs).Prepare counseling materials to help AD patients -especially adolescents- overcome the negative psychological impact of the disease.

5. Discussion

5.1. General overview of the research outcomes

Although AD is often considered a non-serious dermatological disease due to its non- fatal nature (12), our research shows that it imposes a significant burden on adult and adolescent patients, particularly in its severe cases. These studies provide comprehensive evidence on the disease burden components.

While the direct medical costs of AD - often limited to basic topical treatments - are well documented, the hidden burden of the disease is frequently underestimated (61, 84). This hidden burden includes reduced QoL and productivity losses, which when assessed from a societal perspective translate into considerable indirect economic costs (61). Notably, QoL findings reveal a striking average value of up to 20% loss across different countries. This figure is considered exceptionally high for a skin disease. However, the SLR findings show that AD is a debilitating and stressful disease for patients and their families. The chronic daily symptoms - irritation, pain, and continuous discomfort justify this value. This is reflected in the high prevalence of depression and psychiatric comorbidities associated with AD.

Given the high global prevalence of AD, its overall disease burden is comparable, and sometimes exceeds, that of more severe conditions (14). For instance, according to GBD, the age standardized rate of DALYs lost due to AD surpasses that of more severe diseases, such as liver cirrhosis and other chronic liver diseases due to alcohol use. This difference is not attributable to higher burden per individual patient, but rather to the substantial burden across the whole population, and significant impairment in QoL (14).

Based on the GBD 2021 estimates, AD's associated all age DALYs globally was estimated as 5.6 million DALYs. This was comparable to the burden of other non-fatal diseases such as peptic ulcer (6.1 million DALYs), and even higher than other serious disease such as encephalitis (5.0 million DALYs)(85).

5.2. The burden of AD in adults and adolescents globally

The SLR study highlighted the clinical burden of the disease, including its associated comorbidities, signs, and symptoms. It also included data about the factors and disease effects that contribute to each patients' reduced QoL. These clinical and humanistic impacts per patient seem to be consistent across different populations and are not specifically confined to a certain population or geographic area.

Our SLR findings related to humanistic burden are concordant with the findings by Eckert et al. on the burden of AD in adults in several European countries (83). Both studies show that reduction in QoL for AD patients mainly arises from effects such as anxiety, depression, and sleep disorders. Another study also confirms the significant hidden burden of the disease related to QoL losses and loss in productivity (54).

However, other disease burden components vary significantly across different countries. To capture these differences, we conducted studies across several regions.

5.3. Burden cannot be directly compared across countries

When estimating the burden of AD (either direct costs, indirect costs, or QALYs lost) in several countries, it is not logic to use these absolute values to compare across countries. Using these unadjusted values results in false interpretations. For instance, in the MEA study, annual AD direct costs in 2019 in the UAE were estimated at 112.5 million USD, while in Egypt, the annual cost was 42.8 million. This does not mean that AD is more severe or necessarily more common in UAE, since this value is not adjusted to population size or healthcare services costs. When we compared the average annual cost per patient, it showed that costs of treatment in UAE may reach up to 10 times the costs of treatment of AD in Egypt (3,569 USD vs 312 USD). This was the main driver for the high burden in UAE compared to Egypt. These values reflect directly on the burden estimation, creating a larger economic burden in UAE as absolute terms.

The primary objective of our studies was not to conduct comparisons between countries or regions, but to present the individual burden within each country to support local decision-making. Local decision makers are typically not concerned with whether the burden in their

country is higher or lower than in others, they are more focused on reducing the burden within their own country.

For this reason, we avoided direct comparisons among regions, and did not use purchasing power parity to align costs across countries. Nevertheless, in certain cases, we conducted limited comparisons to assess whether a country's burden was notably higher than the average of countries with similar contexts. burden compared to the average of similar settings countries. To do this, we adjusted the cost values relative to each county's GDP. This adjustment allowed us to express the burden as a proportion of the GDP accounting for differences in population size and economic development. These GDP-adjusted values enabled us to identify countries with disproportionately high or low burden levels relative to their economic state.

5.4. Humanistic and economic burden of AD in the MEA region

Our study in the MEA region showed the quantitative values for reduction in QoL (expressed as QALYs lost) in different countries in this region.

This area is of specific interest as it includes countries that share several aspects (e.g. geographical location, climate, culture, language, or level of development), while they are still significantly different in terms of population size, GDP/ capita, and availability of health technologies (86-88) .

When comparing burden of disease components as a percent of GDP in the MEA countries, the results show that the total burden of AD consumes 0.164%-0.265% of the GDP in the included countries, with a wide variability between countries.

Kuwait has the highest total burden of 0.265% of GDP, driven by both the monetary value of QALYs lost valued at 0.189% and a high indirect cost burden of 0.044%. In contrast, the lowest total burden is recorded for Egypt at 0.164%, with close contributions from healthcare costs valued at 0.06% and indirect costs at 0.104%.

The results also bring into focus the heterogeneity on the economic burden that AD presents, depending on a nation's relative indirect productivity costs compared with direct healthcare

costs. In all countries except Egypt, the value of indirect costs due to AD were higher than the direct healthcare costs, reaching up to more than 3 times its value in Saudi Arabia. In Egypt, direct healthcare costs represented the larger proportion of the total economic burden at 63%. This was not attributable to the high health costs, but it to the low indirect costs due to the lower average salary in Egypt compared to the other included countries (89).

In Saudi Arabia, the overall burden of 0.249%, reflected a different pattern, with indirect costs higher at 0.046% than health care costs at 0.013%. Similarly, the UAE has a high total burden of 0.247%, with significant indirect costs of 0.054% and monetary value of QALYs lost at 0.167%. These findings argue for focusing on these burden components in these countries, especially due to the higher value of presenteeism and absenteeism compared to other countries. Algeria reports the lowest economic burden at 0.046% of GDP, but the total burden increases to 0.209% with the significant monetary value of QALYs lost being 0.163%.

The indirect cost burden is highest among the countries in Lebanon, at 0.061%, contributing to a total burden of 0.207%. This shows that there is great societal and economic importance regarding AD, mainly through loss of productivity. These results thus indicate that interventions targeted at reducing absenteeism and presenteeism, coupled with better disease management, may have beneficial effects on mitigating the economic burden in Lebanon and other similar settings.

Although AD only contributes to one component of QALYs lost, as it reduces QoL but does not affect survival, the value of QALYs lost seems to be significant, owing to the high prevalence, and the significantly reduced QoL, especially in more severe stages. The findings show that patients lose approximately 20% of their QoL due to AD, which is alarmingly high for a non-fatal skin disease, especially considering that this figure represents the average AD patient, not just those with severe forms. This substantial impact may be explained by the results of our SLR, which reveal that patients experience additional distressing complications such as night flares, consistent itching, and psychiatric issues, including, in some cases, suicidal ideation. These findings confirm that AD is associated with a significant often hidden burden. The substantial monetary value of QALYs lost in most countries underlines the

urgent need to prioritize interventions that improve patients' QoL and reduce disease-related disability.

This study revealed that a significant proportion of the burden stems from hidden burden components, with direct medical costs accounting for only a small fraction of the total burden. This pattern was consistently observed across all countries included in the study (as illustrated in Table 10), underscoring the need for more attention to the less tangible, but significant aspects of AD's burden, which outweigh the obvious direct medical costs.

Therefore, our next study focused on studying these components.

5.5. Hidden burden of AD in CEE

The study was conducted for Central Eastern European countries to quantify the hidden burden of AD across these countries and provide the policymakers with evidence to inform their decisions on burden reduction strategies, offering insights into the more complex and challenging-to-quantify hidden burden.

Similarly, the results of the hidden burden of AD in CEE study shows the heterogeneity among the various included countries. In absolute terms, Poland had the highest hidden burden of AD with more than 1.1 billion Euros lost annually. Other countries ranged between 42 million to 443 million EUR annually. However, this higher burden is primarily attributable to Poland's larger population compared to other included countries.

In all included countries, the monetary value of QALYs lost represents the larger proportion of total hidden burden, ranging from 87% to 92% of the total hidden burden. This emphasizes the importance of interventions aiming at improving patients' QoL in these countries.

For comparability, values for hidden burden were divided by the GDP per country. Interestingly, the results showed that Estonia had the highest value of total AD hidden cost as a percentage of GDP at 0.43%. This may be due to Estonia's high disease prevalence (2.18%), compared to less than 1.30% in the other CEE countries.

Next comes Hungary, with a hidden cost estimated at 0.26% of GDP, which is far lower compared to Estonia but higher compared to the rest. The next cluster is Croatia, Slovakia,

Lithuania, Czechia, Bulgaria, Poland, and Slovenia, all of which estimated hidden costs at approximately 0.18% of GDP, suggesting a relatively homogenous economic burden of AD within that region. Romania and Latvia have the lowest hidden costs, with 0.12% and 0.11% of GDP, respectively.

This can point out a better integration of the AD management strategies into their healthcare systems or less societal disruption caused by the disease. Alternatively, these figures could reflect underreporting of indirect costs or differences in data collection and methodology.

The CEE study findings align with the study conducted by Augustin et al., which explored the true costs of AD in Europe (61). That study estimated annual indirect costs at 15.2 billion EUR across Europe, while our research places this figure at approximately 3.4 billion EUR for selected CEE countries within the region. This amount reflects the CEE region's proportional share within the broader European context. It is worth noting that Western European countries, with their higher GDP per capita, tend to bear higher absolute costs of the disease burden.

The results are also consistent with the findings of Shin et al. (90), who analyzed global and regional trends in allergic disorders, including AD, using data from the GBD study. Both studies emphasize the substantial humanistic impact of AD. While Shin et al. focused on the global burden, our study highlights its effects within the CEE region. Regarding the humanistic burden, our findings mirror Shin et al.'s observation that the average DALYs for AD have remained relatively stable worldwide, as has the weighted average utility loss.

5.6. Actions to reduce the burden of AD

Our last study was conducted to complement these studies by delivering tangible results, ultimately providing a comprehensive solution for decisionmakers. After quantifying the different burden of disease components, the proposed actions to reduce the burden of AD concludes our research outcomes. Decisionmakers are expected to assess the relative burden of AD within their specific settings and select the potential actions that suits their settings, to reach an ultimate goal of reducing the burden of AD and improving health outcomes for the population.

To reduce the burden of AD, experts advice that focus should be on five domains: capacity building, public awareness, patient support and education, guidelines, and research. Our research provided a list of specific actions in each of these domains. Experts clearly advised that policies that might be successful in specific countries, might not be successful in another. For example, one of the experts panel members advised that, while educating patients to eliminate steroid phobia is a potential action to reduce the burden, this is not essential and useful in his country because there, generally, the phobia of steroids among the patients is uncommon. This emphasizes that before implementation, actions should be assessed and adjusted to country-specific settings.

Experts agreed that effective reduction in the burden of AD will require country-specific action plans for policy interventions to address the needs of the diverse stakeholder groups. They said that it is vital to improve access to more effective treatments for patients, to alleviate the challenges posed by AD. The involvement of healthcare professionals, including dermatologists, general practitioners, pharmacists, and nurses, should be done to provide patient education in each country. Furthermore, social media can be utilized to a large extent to raise public awareness of AD and its management. Cost-effectiveness studies with a broader societal perspective, including indirect costs, are needed for informed decision-making. In addition, counseling materials should be prepared in order to help AD patients, especially adolescents, overcome the negative psychological effects of the disease.

There is no single intervention that is universally effective across all countries. According to the experts' discussions, an intervention that efficiently reduces the burden in one specific settings, may be inefficient or unsustainable in another. This shows the importance of tailored country plans that should be based on local burden patterns, available resources, social and cultural aspects, and health system readiness. Despite this, a universally endorsed intervention domain was the enhancement of patient education. This intervention was advocated by all experts, especially due to its relatively low cost, and potential high impact in alleviating the clinical burden. However, its implementation is still expected to differ significantly across countries, depending on local settings.

5.7. Barriers for implementing evidence-informed policy interventions

Implementing these recommendations faces some barriers at a general system level and at a domain-specific level. At the general system level, challenges include limited budgets, competing health priorities, a shortage of trained personnel, low adherence to clinical guidelines by healthcare providers, inconsistent use of HTA or burden data in decision-making, and a lack of political will.

At the domain-specific level, patient support and education is hindered from factors such as limited time and trained staff, along with a lack of structured programs. Public awareness could be limited due to competing health messaging priorities. Healthcare system capacity is constrained by dermatologist shortages and limited access to modern therapies. Clinical guidelines are often poorly disseminated and inadequately implemented, with limited local adaptation. Finally, research and data domain limitations include scarce funding, fragmented health systems, and weak integration of evidence into policy.

5.8. Research beneficiaries

This research can support a wide range of stakeholders towards efficient allocation of their resources. First, decisionmakers and payers in the included countries can use the country-specific data provided to prioritize interventions and allocate resources efficiently to reduce the burden of AD in their countries. Decisionmakers and payers in other countries can also apply the same estimates to understand and address AD within their own healthcare systems. Additionally, all healthcare decisionmakers can benefit from this research by understanding the global burden and hidden costs of AD in general. Finally, health economists and researchers can leverage the methods used in these studies to conduct similar burden of disease studies for other conditions or other countries.

5.9. Limitations

The limitations identified in our research highlight several challenges in accurately capturing the AD's burden. Heterogeneity in data reporting, with variations in methodologies and severity levels complicated the ability to summarize data accurately and lead to excluding relevant data. Several studies did not mention a clear definition of severity levels, while

severity levels significantly affect the outcomes. Our severity ranks partially overcame this limitation, however, results should be interpreted with caution, as severity is a main contributor to the quantified value of disease burden. We ensured to exclude inconsistent data and to systematically recategorize findings into comparable and homogenous groups, to be able to create accurate estimates.

We kept all our estimates conservative, acknowledging that the actual burden is likely slightly higher than our estimates. Efforts were made to adjust for confounders and minimize inaccuracies to provide a logical and reasonable approximation of the burden.

Although the SLR results were comprehensive, some of its findings had limited applicability, as they primarily discuss global averages. These averages may not significantly support local decisionmakers in implementing targeted strategies to reduce the burden of AD within specific contexts. Recognizing this limitation, our subsequent studies address this gap and provide country-specific data for informed decision making.

Assessing only specific countries in the studied regions is a limitation to these studies. However, this selective approach was intentional, as these regions face significant data gaps in quantifying key components of AD's burden. By focusing on areas with limited data, we aimed to address critical data gaps and provide valuable insights. In regions or contexts with no data gaps, conducting additional research would be unnecessary. For instance, direct healthcare costs of AD were comprehensively covered in the literature by a recent study in Europe (61), eliminating the need to duplicate efforts in quantifying this aspect.

A key limitation is the reliance on international data due to the lack of local data. This approach involves adjusting global data to local demographics, but may fail to reflect exact local nuances, potentially leading to inaccuracies. Methodological challenges, such as using proxy data from other countries also reduces the accuracy of estimates.

We did not evaluate the caregiver burden. While AD caregivers may experience reduced QoL and productivity loss, these are more evident in caregivers for children with AD. However,

in older patients, the effect is minor. Also, there is a lack of sufficient studies providing reliable quantitative values for this burden. Therefore, in line with our conservative approach, we did not include caregiver burden to avoid potential overestimation of the burden due to the scarcity of reliable data.

Prevalence estimates from the GBD study were likely underestimated, as many AD patients may be undiagnosed, leaving a significant portion of the population unaccounted for. Additionally, the exclusion of certain cost components, such as non-medical direct costs, informal caregiving expenses, and the psychological impact on caregivers, might underestimate the burden, however, this is in line with our conservative approach.

Limited representation of lower-income countries, where data collection is sparse, contributes to potential underestimation of the burden in these settings. Underreporting of cases in some countries also likely affects the accuracy of key metrics like prevalence, economic costs, and overall burden.

Additional hidden burden components were not included in our estimations. In line with our conservative approach, we excluded indirect costs beyond productivity losses, as well as intangible costs, such as pain or fear. For instance, barriers to accessing healthcare services, such as difficulty in accessing healthcare facilities or treatments. These challenges create a burden on patients and their caregivers, particularly when timely access to these services is impeded. Such factors still contribute to the total burden, but their effect can be considered negligible in comparison to the major direct and productivity loss indirect costs.

The recommendations provided by our research are primarily general in nature. For each country, a critical final step involves adapting these recommendations to fit the specific national context, including the country's healthcare infrastructure, economic conditions, and population needs. This contextualization is essential to ensure the recommendations are both relevant and effective and relevant in addressing the unique challenges faced by individual countries. Furthermore, while the current evidence on recommendations is not supported by robust evidence on the effectiveness of each intervention, this research was intended to be

exploratory. Nonetheless, the strategies proposed remain actionable and are intended to serve as a foundation for future policy initiatives, including targeted policy trials and evaluations that can rigorously measure the impact of each proposed action.

We assume these minor inaccuracies would not affect the validity of our results. It is important to note that burden of disease studies are not designed to deliver perfectly accurate figures; rather, they aim to provide a rough estimate of the burden's magnitude. This approximation is intended to be sufficient for informing policymakers and guiding decisions related to resource allocation and intervention strategies.

5.10. Future research recommendations

This research highlights the necessity of conducting similar comprehensive burden of disease studies across various disease areas. Conducting such studies at a country-specific level is essential to provide useful local data. These insights considered crucial tools for decisionmakers to effectively implement HTA, and to use the available resources efficiently.

6. Conclusions

AD is a very prevalent dermatological disease that has several stages. Without quantification, the disease seems to be a simple, non-fatal dermatological condition with a low comparative burden among other disease areas. Therefore, experts are usually not concerned with allocating resources to mitigate such a simple disease and are not interested in exploring potential actions to reduce that burden.

Our research findings reveal the unexpectedly significant burden of AD, that is comparable to much more severe diseases. This high burden stems from two main factors: the very high prevalence of the disease, and the hidden burden through effects on reducing productivity and QoL.

It might be assumed that reduction in QoL due to AD is minor, while the research findings reveal that around 20% of the QoL of an average adult or adolescent patient is lost due to AD with an average annual utility loss per patient of 0.205 to 0.209.

Economic burden of the disease is significantly different among patients in different countries. However, the common finding is that AD's indirect costs are usually much more than its simple direct costs, and that reducing absenteeism or presenteeism for patients would result in preventing a significant proportion of the burden.

In all countries studied, hidden burden components were the major contributors to the disease burden, further emphasizing that the disease burden is usually underestimated.

Simple actions can significantly reduce the substantial disease burden. According to health policy experts, actions like educating patients, and public awareness will have an impact on reducing the burden, with minimal additional costs.

Decisionmakers are recommended to use the findings of this study to assess the burden in their countries and use the policy actions and recommendations list to tailor a specific action plan and ultimately reduce the burden of AD effectively.

7. Summary

AD is a chronic inflammatory skin disease that significantly affects adolescents and adults. Given the high prevalence of AD and its non-fatal nature, it is usually deprioritized among disease areas for resource allocation.

This research, however, shows that AD's impact is substantial in adults and adolescents. This is primarily attributable to hidden burden components, such as productivity loss and reduced QoL. Additionally, AD also imposes an economic burden on healthcare systems and societies.

We aimed to comprehensively assess the burden of AD in adults and adolescents. A systematic literature review was conducted to evaluate the global clinical, economic, and humanistic burdens of AD. The findings provided insights about QoL loss, disability-adjusted life years, and economic burden. Based on this, region-specific studies were conducted to quantify AD's burden in the MEA region, and in CEE. These studies showed the significant effects of indirect costs and the huge societal burden due to lost productivity and reduced QoL.

Humanistic burden is a major contributor to the total AD burden in Middle East-Africa, and CEE countries, reaching up to several multiples of the value of the economic burden. Indirect costs are also much higher than direct medical costs of the disease, reaching up to 70% of the total economic burden in countries like Saudi Arabia, South Africa, and Lebanon.

In addition to burden of disease quantification, this research proposed actions to reduce AD's burden. We identified potential policy interventions through a literature search, complemented by an expert panel. Experts recommended that these interventions should be tailored to each country, based on its challenges and healthcare system structure.

The findings of our studies help to inform decisionmakers on the actual disease burden, emphasizing the major contribution of the hidden burden to the total burden. Interventions should be taken to mitigate this burden through allocating the available resources effectively toward reducing AD's societal and economic impacts.

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11. Appendices

Table S1 A summary of databases searched in the SLR

Database	Short summary	Link
PubMed	A comprehensive database maintained by the National Library of Medicine, providing access to millions of references from biomedical and life sciences journals, including MEDLINE.	https://pubmed.ncbi.nlm.nih.gov/
Scopus	A multidisciplinary abstract and citation database that covers peer-reviewed literature across science, technology, medicine, social sciences, and arts and humanities.	https://www.scopus.com/
Cochrane Library	A collection of high-quality, independent evidence to inform healthcare decision-making, including systematic reviews from the Cochrane Collaboration.	https://www.cochranelibrary.com/
Centre for Reviews and Dissemination (CRD)	A UK-based database providing systematic reviews and economic evaluations focused on health interventions and policy.	https://www.york.ac.uk/crd/
EconPapers	An online resource offering access to a comprehensive collection of working papers, journal articles, and software components in economics.	https://econpapers.repec.org/
ISPOR Scientific Presentations Database	A repository of abstracts and presentations from ISPOR conferences, focusing on health economics and outcomes research.	https://www.ispor.org/heor-resources/presentations-database/search

NICE (National Institute for Health and Care Excellence)	An independent public body in the UK, providing national guidance and advice to improve health and social care, with a focus on health technology assessment.	https://www.nice.org.uk/
CADTH (Canadian Agency for Drugs and Technologies in Health)	A Canadian organization that delivers evidence-based information on the clinical effectiveness, cost-effectiveness, and impact of health technologies to support informed healthcare decisions.	https://www.cda-amc.ca/

Table S2 Systematic Literature Review Search Strategy

Search strings in Scopus Conducted on December 3, 2020				
Domain	**Subcategory**	**Search**	**Search term "Scopus"**	**Number of hits**
Disease	Atopic dermatitis	#1	TITLE-ABS-KEY ("atopic dermatitis" OR "eczema" OR "atopic eczema" OR "Prurigo Besnier") AND ("atopic dermatitis" OR "atopic eczema" OR "Prurigo Besnier")	46,896 hits
Burden		#2	TITLE-ABS-KEY ("morbidity" OR "mortality" OR "morbidities" OR "mortalities" OR "death" OR "deaths" OR "burden" OR "burden of disease" OR "burden of illness" OR "humanistic burden" OR "clinical burden" OR "life years lost" OR "premature mortality" OR "quality adjusted life years" OR "QALY" OR "disability adjusted life years" OR "DALY" OR "quality of life" OR "QoL" OR "health related quality of life" OR "HRQOL" OR "health-related quality of life" OR "life quality" OR "economic burden" OR "cost burden" OR "resource burden" OR "financial burden" OR "economic consequences" OR "cost of illness" OR "healthcare cost" OR "cost of disease" OR "cost analysis" OR "cost assessment" OR "cost study" OR "resource use" OR "healthcare resources" OR "resource utilization" OR "expenditure" OR "out of pocket" OR "patient cost" OR "co-payment" OR "private expenditure" OR "patient time" OR "caregiver cost" OR "caregiver time" OR "caregiver cost" OR "caregiver time" OR "societal cost" OR "social cost" OR "social care cost" OR "work loss" OR "absenteeism" OR "presenteeism" OR "productivity loss" OR "lost productivity" OR "earnings" OR "educational attainment" OR "educational achievement" OR "educational impairment" OR "occupational attainment" OR "occupational achievement" OR "occupational impairment" OR "social functioning" OR	3,791,142 hits

			"social impairment" OR "caregiver burden" OR "family burden" OR "indirect costs")	
#1 AND #2				5072 hits
Limit to “English”				4517 hits
From 2011				3192 hits
TITLE-ABS-KEY ("atopic dermatitis" OR "eczema" OR "atopic eczema" OR "Prurigo Besnier") AND ("atopic dermatitis" OR "atopic eczema" OR "Prurigo Besnier") AND TITLE-ABS-KEY ("morbidity" OR "mortality" OR "morbidities" OR "mortalities" OR "death" OR "deaths" OR "burden" OR "burden of disease" OR "burden of illness" OR "humanistic burden" OR "clinical burden" OR "life years lost" OR "premature mortality" OR "quality adjusted life years" OR "QALY" OR "disability adjusted life years" OR "DALY" OR "quality of life" OR "QoL" OR "health related quality of life" OR "HRQOL" OR "health-related quality of life" OR "life quality" OR "economic burden" OR "cost burden" OR "resource burden" OR "financial burden" OR "economic consequences" OR "cost of illness" OR "healthcare cost" OR "cost of disease" OR "cost analysis" OR "cost assessment" OR "cost study" OR "resource use" OR "healthcare resources" OR "resource utilization" OR "expenditure" OR "out of pocket" OR "patient cost" OR "co-payment" OR "private expenditure" OR "patient time" OR "caregiver cost" OR "caregiver time" OR "caregiver cost" OR "caregiver time" OR "societal cost" OR "social cost" OR "social care cost" OR "work loss" OR "absenteeism" OR "presenteeism" OR "productivity loss" OR "lost productivity" OR "earnings" OR "educational attainment" OR "educational achievement" OR "educational impairment" OR "occupational attainment" OR "occupational achievement" OR "occupational impairment" OR "social functioning" OR "social impairment" OR "caregiver burden" OR "family burden" OR "indirect costs") AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011))				Final search term
Search strings in Medline (through PubMed) Conducted on December 3, 2020				
Domain	**Subcategory**	**Search**	**Search term “PubMed”**	**Number of hits**

Disease	Atopic dermatitis	#1	("atopic dermatitis" OR “eczema” OR "atopic eczema" OR "Prurigo Besnier”) (Title/ abstract)	36,422 hits
		#2	("atopic dermatitis" OR "atopic eczema" OR "Prurigo Besnier”) (All fields)	29,159 hits
		#3	#1 AND #2	24,743 hits
Clinical burden		#4	“morbidity” OR “mortality” OR “morbidities” OR “mortalities” OR “death” OR “deaths” (Title/ abstract)	1,630,126 hits
Health related quality of life burden		#5	“burden” OR “burden of disease” OR “burden of illness” OR “humanistic burden” OR “clinical burden” OR “life years lost” OR “premature mortality” OR “quality adjusted life years” OR “QALY” OR “disability adjusted life years” OR “DALY” or “quality of life” OR “QoL” or “health related quality of life” or “HRQOL” or “health-related quality of life” or “life quality”	496,086 hits
Economic burden	Direct healthcare cost	#6	“economic burden” OR “cost burden” OR “resource burden” OR “financial burden” OR “economic consequences” OR “cost of illness” OR “healthcare cost” OR “cost of disease” OR “cost analysis” OR “cost assessment” OR “cost study”	33,479 hits
	Direct patient and caregiver cost	#7	“resource use” OR “healthcare resources” OR “resource utilization” OR “expenditure” OR “out of pocket” OR “patient cost” OR “co-payment” OR “private expenditure” OR “patient time” OR “caregiver cost” OR “caregiver time” OR “caregiver cost” OR “caregiver time”	72,614 hits
	Wider societal (and intangible) cost	#8	“societal cost” OR “social cost” OR “social care cost” OR “work loss” OR “absenteeism” OR “presenteeism” OR “productivity loss” OR “lost productivity” OR “earnings” OR “educational attainment” OR “educational achievement” OR “educational impairment” OR “occupational attainment” OR “occupational achievement” OR	44,505 hits

			“occupational impairment” OR “social functioning” OR “social impairment” OR “caregiver burden” OR “family burden” or “indirect costs”	
#9			#4 OR #5 OR #6 OR #7 OR #8	2,127,246 hits
#3 AND #9				2171 hits
Applied filter “English”				2039 hits
Limit from 2011				1487 hits
Search strategy in Cochrane Search on December 6, 2020, through https://www.cochranelibrary.com/advanced-search				
Search term				**hits**
("atopic dermatitis" OR "eczema" OR "atopic eczema" OR "Prurigo Besnier"):ti,ab,kw AND ("morbidity" OR "mortality" OR "morbidities" OR "mortalities" OR "death" OR "deaths" OR "burden" OR "burden of disease" OR "burden of illness" OR "humanistic burden" OR "clinical burden" OR "life years lost" OR "premature mortality" OR "quality adjusted life years" OR "QALY" OR "disability adjusted life years" OR "DALY" or "quality of life" OR "QoL" or "health related quality of life" or "HRQOL" or "health-related quality of life" or "life quality" OR "economic burden" OR "cost burden" OR "resource burden" OR "financial burden" OR "economic consequences" OR "cost of illness" OR "healthcare cost" OR "cost of disease" OR "cost analysis" OR "cost assessment" OR "cost study" OR "resource use" OR "healthcare resources" OR "resource utilization" OR "expenditure" OR "out of pocket" OR "patient cost" OR "co-payment" OR "private expenditure" OR "patient time" OR "caregiver cost" OR "caregiver time" OR "caregiver cost" OR "caregiver time" OR "societal cost" OR "social cost" OR "social care cost" OR "work loss" OR "absenteeism" OR "presenteeism" OR "productivity loss" OR "lost productivity" OR "earnings" OR "educational attainment" OR "educational achievement" OR "educational impairment" OR "occupational attainment" OR "occupational achievement" OR "occupational impairment" OR "social functioning" OR "social impairment" OR "caregiver burden" OR "family burden" or "indirect costs"):ti,ab,kw AND ("atopic dermatitis" OR "atopic eczema" OR "Prurigo Besnier")				24 cochrane reviews
Search strings in ISPOR scientific presentations database Search on December 6, 2020, through https://www.ispor.org/heor-resources/presentations-database/search				
Search term				**hits**
"atopic dermatitis" OR "atopic eczema"				169 hits
Limit to after years (2011-2020)				119 hits

Search strategy in EconPapers Search on December 6, 2020, through https://econpapers.repec.org/scripts/search.pf	
Search term	**hits**
"atopic dermatitis" OR "atopic eczema"	48 hits
Limit to after years (2011-2020)	45 hits
Search strategy in CRD Search on December 6, 2020, through https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp	
Search term	**hits**
Any field: "atopic dermatitis" OR "atopic eczema" and limit years from 2011 to 2020	50 hits
Search strategy in websites of HTA agencies (NICE, CADTH) NICE: Search on December 6, 2020, through https://www.nice.org.uk/about/what-we-do/evidence-services/journals-and-databases	
Search term	**hits**
"atopic dermatitis" OR "atopic eczema"	40 hits
CADTH: Search on December 6, 2020, through https://www.cadth.ca/	
Search term	**hits**
atopic dermatitis	27 hits[a]
Eczema	35 hits[a]
disseminated neurodermatitis	1 hit[a]

[a]Those numbers do not do not sum to the total hits found in CADTH because there were several duplicates

Table S3 Details of data adjustment approaches conducted

Type of Data Variation	**Adjustment Made**
Currency	All cost values were converted to USD using the relevant currency exchange rates at the time of data collection and adjusted to 2020 values using the Consumer Price Index (CPI).
Timeframe	All cost data reported in non-annual timeframes were standardized by converting to annual costs to ensure comparability across studies.
Cost Classification	Cost data were consistently reclassified into the following categories for uniformity:

	• Total Costs: Combined direct and indirect costs. • Direct Costs: All direct healthcare-related expenses, including outpatient visits, hospitalizations, topical and systemic therapies, and phototherapy. • Indirect Costs: Productivity losses related to absenteeism or presenteeism due to atopic dermatitis (AD).
Severity Levels	Severity levels were standardized into a 5-point ordinal scale (1 = mild, 5 = severe), as outlined in Section 3.2.5.
Patient Classification	Patient groups were reclassified or renamed, where applicable, to align similar categories for more consistent and meaningful comparative analysis.

Table S4 Detailed number of AD patients in the selected Countries in MEA region subgrouped by age group and gender*

Country	**Algeria**		**Egypt**		**KSA**		**Kuwait**		**Lebanon**		**South Africa**		**UAE**	
Age group	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
10 to 14	25,988	32,816	48,804	60,195	18,640	21,330	2,007	2,517	3,126	3,722	42,036	50,386	2,964	3,706
15-19	17,904	22,832	34,046	42,883	16,869	17,833	1,398	1,745	2,085	2,463	27,328	32,264	2,053	2,535
20-24	18,210	23,847	30,646	41,089	20,470	21,173	1,705	2,163	2,081	2,484	19,381	23,244	1,869	2,252
25-29	20,044	26,800	27,648	38,316	24,164	24,179	2,324	3,087	2,649	3,395	15,609	19,306	2,939	1,942
30-34	19,436	26,761	24,944	34,025	26,980	24,901	3,024	4,137	2,468	3,526	12,584	15,256	13,776	3,842
35-39	16,455	22,944	21,074	28,364	24,981	21,059	2,829	3,324	1,802	2,776	9,771	11,670	12,362	6,714
40-44	11,961	16,731	15,363	20,491	18,771	15,256	2,268	2,438	1,236	2,054	7,485	9,127	10,528	3,506
45-49	8,833	12,464	10,817	14,403	11,350	9,763	1,408	1,571	983	1,666	6,116	8,163	5,489	1,868
50-54	6,353	8,953	8,100	10,956	5,915	5,600	919	932	697	1,207	4,969	7,134	2,741	990
55-59	4,458	6,189	5,931	8,062	3,412	3,310	469	484	541	922	4,376	6,745	1,102	494
60-64	3,070	4,244	4,108	5,302	1,908	1,866	268	252	349	617	3,695	5,957	526	260
65-69	2,144	2,868	2,688	3,448	1,083	986	121	131	272	473	2,714	4,546	214	109
70-74	1,197	1,700	1,603	1,910	590	494	95	76	209	356	1,770	3,138	59	44
Total AD population	**156,053**	**209,150**	**235,771**	**309,446**	**175,133**	**167,752**	**18,836**	**22,856**	**18,497**	**25,663**	**157,835**	**196,936**	**56,623**	**28,262**
Total both sexes	**365,204**		**545,217**		**342,885**		**41,691**		**44,161**		**354,771**		**84,885**	

*Source: GBD results tool 2019 (46)

Table S5 Direct healthcare costs questionnaire used in the MEA expert interviews

		Mild diagnosed			Moderate			Severe/Resistant			[redacted]				Comments
	Prevelance														
	Outpatient/Inpatient visits														
		Proportion (%)	Frequency/year		Proportion (%)	Frequency/year		Proportion (%)	Frequency/year				Price/visit or per day	Price /year	
	Dermatologist/Allergist specialist visit			[redacted]			[redacted]			[redacted]					
	Emergency department visits														
	Hospital stay due to complications/ days														
	Other??														
	Medications														
Topical	*Drug name*	*Proportion %*	*Dose/number of boxes per month*	*Number of months*	*Proportion %*	*Dose/number of boxes per month*	*Number of months*	*Proportion %*	*Dose/number of boxes per month*	*Number of months*	*Size of box*	*Unit*	*Price/Box*	*Price/year*	
	Emolients (ex. Emo soft cream/Nivea soft cream/Glysolid cream/Panthenol cream/La roche Lipikar)														
	Topical Corticosteroids (TCS)														
	Low potency TCS (ex. Hydrocortisone 1%)														
	Medium Potency TCS (ex. Betamethasone /Betaderm/Texacort)														
	High Potency TCS														
	Topical Calcineurin inhibitors (TCIs) (ex. Treczims, Tarolimus)														
	Topical PDE4 inhibitors														
Systemic	*Drug name*	*Proportion %*	*Dose/day (No. of tablets/ injections per day)*	*How long? (Days / year)*	*Proportion %*	*Dose/day (No. of tablets/ injections per day)*	*How long? (Days / year)*	*Proportion %*	*Dose/day (No. of tablets/ injections per day)*	*How long? (Days / year)*	*Size of box (no. of tablets/ no. of injections)*		*Price/Box*	*Price/year*	
	Systemic Antihistamines (ex. Zyrtec/Levohistam/Telfast 120 mg)														
	Systemic Corticosteroids (ex. Solupred 20mg)														
	Systemic immunosuppressants (ex. Cyclosporine)														
														0	
	Montelukast sodium (ex. Singulair 10mg)														
														0	
	Antibiotics (ex. Augmentin)														
														0	
Others	Phototherapy (ex. Narrow band UVB)														
														0	
	Other (ex. Omazilumab)														
														0	

Table S6: Estimated number of patients in CEE countries by age group (2022 estimate)*

Age group	Poland	Hungary	Romania	Czechia	Bulgaria	Slovakia	Croatia	Estonia	Lithuania	Slovenia	Latvia
10-14	43,821	17,400	18,586	13,891	7,764	6,825	5,025	5,219	3,695	2,479	1,807
15-19	27,572	11,553	10,807	7,592	4,746	4,277	3,270	2,711	2,361	1,510	914
20-24	21,192	8,393	6,828	5,109	3,084	3,250	2,591	1,717	1,737	1,088	533
25-34	36,969	12,544	10,558	9,542	5,763	5,629	3,608	3,132	2,607	1,803	986
35-44	37,716	14,505	11,462	10,654	6,060	5,749	3,620	2,760	2,160	1,996	804
45-54	30,846	13,138	12,738	10,118	6,244	4,993	3,784	2,672	2,707	2,039	954
55-64	35,515	12,306	11,914	9,261	6,339	5,203	4,168	2,763	2,963	2,135	1,145
65-74	29,384	11,345	10,778	9,562	6,192	4,172	3,392	2,167	2,090	1,688	912
Above 75	19,350	8,534	7,857	6,441	4,322	2,546	2,809	2,033	2,077	1,488	817
Total AD population	**282,363**	**109,718**	**101,527**	**82,171**	**50,513**	**42,643**	**32,266**	**25,173**	**22,397**	**16,225**	**8,872**

*Source: GBD results tool 2022 (46)

Table S7 Estimated EQ-5D index population norm values for Poland

Age range	**Males**	**Females**
18–24	0.953	0.950
25–34	0.950	0.940
35–44	0.924	0.927
45–54	0.891	0.876
55–64	0.858	0.855
65–74	0.843	0.805
75+	0.781	0.731

Source: Zrubka Z, Golicki D, Prevolnik-Rupel V, Baji P, Rencz F, Brodszky V, Gulácsi L, Péntek M. Towards a Central-Eastern European EQ-5D-3L population norm: comparing data from Hungarian, Polish and Slovenian population studies. Eur J Health Econ. 2019 Jun;20(Suppl 1):141-154. doi: 10.1007/s10198-019-01071-0. Epub 2019 May 17. PMID: 31102159; PMCID: PMC6544754.

Table S8 Search term used for searching potential policy interventions

Domain	**Search terms**
AD domain	*("Atopic dermatitis" OR "Atopic eczema" OR "eczema")*
Policy actions	*("white paper" OR "policy" OR "policies" OR "reducing the burden" OR "reducing burden" OR "patient education" OR "social support" OR "decision makers" OR "policymakers" OR "early prevention" OR "support group" OR "support groups")*

Table S9 Multivariate regression model for utility of patients with AD

Parameter	**Beta coefficient (β)**	**Standard error**	**95% Wald Confidence interval**		**Hypothesis test**		
			Lower	**Upper**	**Wald chi-squared**	**Degrees of freedom (df)**	**Significance**
(Intercept)	1.348	0.2433	0.871	1.825	30.675	1	0.000
Severity rank = 2	0.108	0.0256	0.058	0.158	17.746	1	0.000
Severity rank = 3	0.086	0.0504	-0.013	0.185	2.925	1	0.087
Severity rank = 4	0[a]						

Age, years	-0.005	0.0031	-0.011	0.001	2.626	1	0.105
% of males	-0.863	0.2772	-1.406	-0.319	9.686	1	0.002
Scale	0.001[b]	0.0006	0.001	0.003			
Dependent variable: quality of life							
a Set to zero because this parameter is redundant							
b Maximum-likelihood estimate							

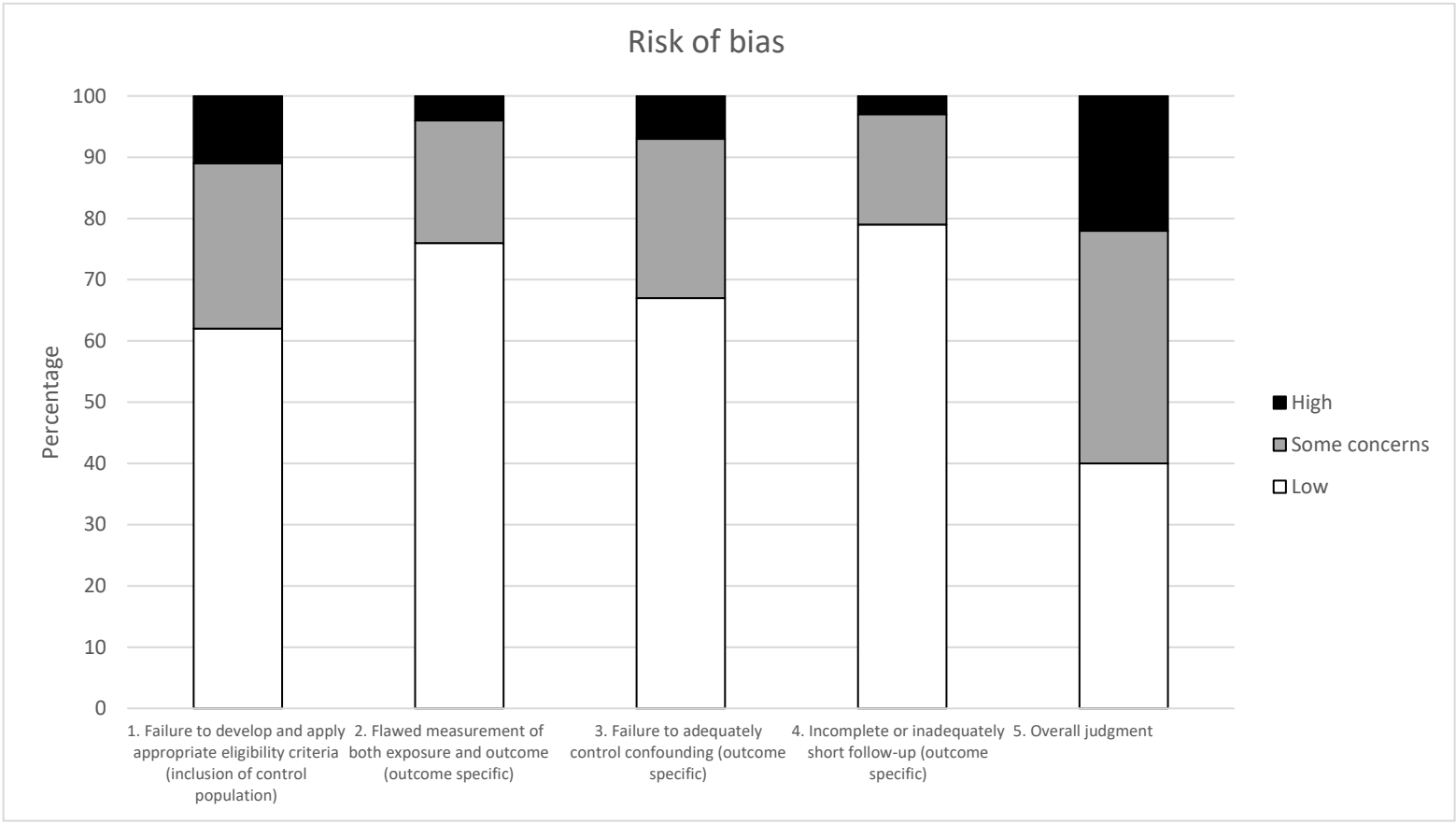

Figure S1 Summary of the risk of bias assessment results of included studies in the systematic literature review

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REVIEW

Burden of Atopic Dermatitis in Adults and Adolescents: a Systematic Literature Review

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ABSTRACT

Introduction: Although previously regarded as a children's disease, it is clear that atopic dermatitis (AD) is also highly prevalent in adults. Because AD is not associated with mortality, it is usually neglected compared with other, fatal diseases. However, several studies have highlighted that AD burden is significant due to its substantial humanistic burden and psychosocial effects. This study aims to summarize and quantify the clinical, economic, and humanistic burden of AD in adults and adolescents.

Methods: A systematic literature search was performed in PubMed, Scopus, Cochrane, Centre for Reviews and Dissemination (CRD), EconPapers, The Professional Society for Health Economics and Outcomes Research (ISPOR), The National Institute for Health and Care Excellence (NICE), and The Canadian Agency for Drugs and Technologies in Health (CADTH). Studies were included if they reported clinical, economic, or humanistic effects of AD on adults or adolescents, from January 2011 to December 2020. The Grading of Recommendations Assessment tool was used to assess risk of bias for the included studies. Regression models were used to explain the correlation between factors such as disease severity and quality of life (QoL).

Results: Among 3400 identified records, 233 studies were included. Itch, depression, sleep disturbance, and anxiety were the most frequently reported parameters related to the clinical and humanistic burden of AD. The average utility value in studies not stratifying patients by severity was 0.779. The average direct cost of AD was 4411 USD, while the average indirect cost was 9068 USD annually.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-022-00819-6.

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Conclusions: The burden of AD is significant. The hidden disease burden is reflected in its high indirect costs and the psychological effect on QoL. The magnitude of the burden is affected by the severity level. The main limitation of this study is the heterogeneity of different studies in terms of data reporting, which led to the exclusion of potentially relevant data points from the summary statistics.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis is a very common skin disease among children and adults. The disease is nonfatal but may lead to patients and families having a low quality of life and decreased productivity, especially in its severe state. Because atopic dermatitis is more common in children than adults, most published research is directed to studying the effect of the disease on children. Atopic dermatitis affects patients' health, quality of life, financial state, and productivity. Therefore, our study aims to study and quantify the burden caused by the disease represented in the clinical burden, humanistic burden, and economic burden. We conducted a systematic literature review to determine all relevant studies providing specific values for the burden. The studies included are those providing information on the percentage of patients affected by specific symptoms, costs paid for treatment, number of days of productivity lost due to the disease, and quality-of-life questionnaire results for patients with atopic dermatitis or their caregivers. We analyzed the data from all relevant studies to calculate average values and quantify the burden. The results of our study should help healthcare sector decision-makers in understanding the real effect of the disease on adults and adolescents and rearrange their priorities for treating different diseases based on the specific burden of each disease.

Keywords: Atopic dermatitis; Atopic eczema; Burden of disease; Clinical burden; Dermatology; Economic burden; Humanistic burden; Systematic literature review

Key Summary Points
The burden of atopic dermatitis is significant, mainly owing to its high prevalence.
Itch, depression, sleep disturbance, and anxiety are the most common manifestations among atopic dermatitis patients.
Managing each atopic dermatitis patient costs about 4411 USD annually.
Indirect costs (productivity lost costs) of atopic dermatitis represent more than double its direct costs.
The quality of life of patients with atopic dermatitis is significantly affected by the disease, but the effect is largely dependent on the severity level.

INTRODUCTION

Atopic dermatitis (AD) is a nonfatal disease that significantly impairs patients' quality of life (QoL). According to the global burden of disease study, AD has the highest disability-adjusted life-year (DALY) burden among all skin diseases. Its burden is ranked in the top 15 among all nonfatal diseases, and it is responsible for 0.36% of the total DALY burden of all 359 diseases and injuries analyzed in the study [1]. Compared with other dermatological diseases, AD poses a significantly higher burden. The age-standardized DALY rate of AD is 75% higher compared with psoriasis and 82% compared with urticaria, representing more than twice the burden of any other skin disease [1].

AD is also known as atopic eczema [2] and is a chronic disease that causes painful flares of inflamed, dry, and itchy skin periodically. Patients with AD usually have accompanying

allergic disease, such as asthma or hay fever. To date, no cure has been found for AD, but treatments and self-care measures can relieve itching and prevent new outbreaks significantly [3].

Patients with moderate to severe AD often experience flares that negatively affect their productivity at work or school [4]. A cross-sectional study in Iran reported that 50% of dermatology patients suffered from psychiatric comorbidities as well [5]. An international study reported that 32% of participants believed that AD affected their school or work life, and 14% of participating adults believed that their career progression had been hindered by AD [4].

The prevalence of AD started to increase in the last decades of the twentieth century [6], with a prevalence up to 10–20% in children. Although AD had been regarded as a children's disease, it has become clear that many adults also are affected, with an estimated prevalence of 3–5% in the general population [7].

Estimating the burden of AD on the basis of scientific evidence can help decision-makers make more informed treatment decisions. Understanding the burden of AD may also support public health policies, help to prioritize interventions, and allow for better resource allocation [8]. AD is a nonfatal disease and therefore usually neglected compared with more severe or fatal diseases. However, several studies have highlighted that the burden of AD is significant because of the substantial humanistic burden and psychosocial effects it can cause [9–11].

The aim of this systematic review is to summarize and quantify the clinical, economic, and humanistic burden of AD in adults and adolescents.

METHODS

Databases and Literature Search Strategy

We conducted a systematic literature review (SLR) and reported its results according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting SLRs [12]. We searched PubMed, Scopus, the Cochrane library, Centre for Reviews and Dissemination (CRD), and EconPapers for relevant studies. Additionally, grey literature sources were searched, including The Professional Society for Health Economics and Outcomes Research (ISPOR) scientific presentations database, and websites of health technology assessment agencies [The National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH)]. The search terms were constructed based on two domains: "Atopic dermatitis "and "Burden of disease." To identify suitable keywords for the search term, Medical Subject Headings (MeSH) terms, Google search, and previous papers on the same topic were used as guidance. These helped to identify relevant search terms and their thesaurus.

We included studies that evaluated any type of burden related to AD. Because the burden of disease is dependent on factors such as prevalence and available treatment options, which vary significantly within 10 years, the literature search was limited to studies published since January 2011. The search was restricted to English-language papers. Although our review focused on adults and adolescents, no age restriction was applied during the literature search to avoid missing potentially relevant studies that were not labeled as containing data for a specific age group. Instead, studies not reporting any data on patients older than 10 years were excluded during the screening and full-text review phases. The detailed search strategy is described in Supplementary Table S1.

Owing to the overlap between databases, search results were first de-duplicated using the embedded feature of EndNote software version X9. Additional duplicates were manually identified and excluded during the screening phase. The snowballing technique was used to add relevant studies from the references cited in the papers found during the SLR. In case of eligibility, the pool of included papers was extended.

Title and Abstract Screening

Studies identified during the literature search were screened by two independent researchers

through title and abstract screening. Disagreements were resolved by a third principal researcher. As a first step, the titles and abstracts of all studies were screened using the following predefined exclusion criteria: (1) duplicates, (2) no English abstract, (3) published before 1 January 2011, (4) letters, editorial, case reports, nonsystematic reviews, or animal studies, (5) not related to AD or eczema, (6) not reporting data for patients 10 years or older, and (7) not evaluating the clinical, economic, or humanistic burden of AD (e.g., those investigating treatment efficacy).

Full-Text Screening and Data Extraction

Studies that were eligible for inclusion from the title and abstract screening phase were downloaded, and their full texts were screened. The same previously mentioned exclusion criteria were used, in addition to excluding inaccessible studies and studies with experimental study designs (e.g., clinical trials) because they do not reflect the real-life burden. Other reasons for exclusion were studies in which AD was a comorbidity with other diseases [13] or if there was a confounding effect of a drug other than the usual treatment [14]. In these cases, the burden reported was not solely dependent on AD.

For the included studies, data were extracted in Microsoft Excel. Extracted data were validated by another independent researcher. The general information extracted included number of patients, average age, sex distribution, type of study, and most importantly, whether the study included information about any of the four domains: QoL scoring, humanistic burden other than QoL score, clinical burden, and economic burden. The included studies had data about at least one of the four domains. Risk-of-bias assessment of the studies was performed using the Grading of Recommendations Assessment (GRADE) tool [15]. Each study was assessed for risk of bias by one researcher and revised by another. In case of disagreement, the two researchers discussed to reach a valid decision. A summary of the quality assessment results is shown in Supplementary Fig. S1.

Because of the heterogeneity of the data collected, each domain was extracted in a separate Microsoft Excel sheet. In the clinical and humanistic burden sheets, data were extracted based on the conceptual model developed by Grant et al. [16] to illustrate the clinical and humanistic burden associated with AD in adults and adolescents. Data about signs and symptoms, as well as psychological impact and health-related QoL (HRQoL) impact, were extracted as "mentioned" or "not mentioned." The number of unique studies reporting the specific impact as part of the results was calculated. In case a clinical questionnaire or assessment tool was used, details were extracted in a multirow format, including subgroup details. Similarly, QoL questionnaire results were extracted. The economic data reported were also extracted in a multirow format, including data about costs, healthcare resource utilization (HCRU), and productivity lost.

Grant et al. [16] categorized the impact of AD as signs, symptoms, mediating factors, proximal impact, and distal HRQoL impact. We adapted the model by recategorizing the same domains under clinical and humanistic burden. Based on the adapted model, clinical burden subgroups were considered to cover psychological impact, signs, and symptoms: (1) psychological impact (depression, anxiety, stress, suicidal ideation, other psychological manifestation), (2) signs (itch or pruritis, burning or heat or tingling sensation, skin sensitivity/sensitivity to sun, soreness/pain/tenderness, skin irritation, skin tightness), and (3) symptoms [redness (erythema), dryness (xerosis), bumps/blisters/papules/vesicles, hardening/flaking, cracking/fissuring, scaling/peeling, thickening/lichenification, bleeding, edema/swelling, other symptoms]. Psychological impact parameters were extracted in both clinical and humanistic burden because they were noted to affect both domains in the studies.

The humanistic burden subgroups included (1) mediating factors (scratching, skin picking), (2) proximal impact (sleep disturbance, lack of concentration, bodily/physical discomfort), (3) distal HRQoL impact (limitation in daily activity, psychological impact, physical limitation, limitation in social/leisure activities, limitation

in role: work, limitation in role: school, problems with interpersonal relationships, problems with sexual functioning, suboptimal skin-related health perceptions/cognition, financial burden associated with buying special products), and (4) other humanistic burden manifestations.

Data Processing and Analysis

Simple statistics were obtained from the extracted data, including average number of patients, average study duration, type of data sources, and average age of patients. Frequency of articles by region and income groups was calculated based on the World Bank classification (June 2019 update) [17].

The frequency of mentions of the humanistic and clinical impact is reported, and the details of the clinical burden are narratively summarized. Further in-depth analysis was conducted for QoL and economic data. For this purpose, each type of data underwent processing as elaborated below.

Disease Severity

Reporting of disease severity in different studies was heterogeneous and used different terminologies that hindered the ability to assess severity as an independent variable, so severity ranks from different publications were transformed into an ordinal scale ranging from 1 to 5, where a higher value indicates higher severity. In case a study featured only two severity groups, the less severe group was labeled 2 and the more severe group was labeled 4, while if the study mentioned three subgroups, the subgroups were labeled 2, 3, and 4. In case of four severity groups the labels were 1, 2, 4, and 5, while in the case of five severity subgroups, the groups were labeled from 1 to 5. Studies reporting the whole population without specifying severity levels were excluded from the ordinal scale and labeled as "unstratified population."

Economic Data

Economic data were converted to annual cost per patient values when possible. For studies reporting the time horizon as lifetime, the estimated life expectancy of patients was used (average age of death of AD patients – average age at onset) [18, 19]. Furthermore, for cost data, values were adjusted to inflation using the consumer price index (CPI) for 2020 from the World Bank database. If CPI values for the year 2020 were not available, the most recently reported values were used instead [20]. If more than one country was included explicitly in the study, the average CPI of all included countries was used. The CPI for Taiwan was not available, so it was obtained from an external source [21]. Next, values were converted to 2020 USD using the official exchange rate from the World Bank database [22].

QoL Data

Studies measured QoL using different questionnaires or scales. We unified QoL results into one unit to allow for aggregation of results and comparison. Utility values have reference points of 0 and 1, where 0 indicates death and 1 indicates perfect health. The European QoL Five Dimension (EQ-5D) index questionnaire is the QoL questionnaire that provides values on a utility scale, so the QoL values identified using other scales were transformed (i.e., mapped) to EQ-5D index values when possible.

Studies using the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (cDLQI) questionnaire results were transformed to the EQ-5D index using an online transformation tool [23] To transform EQ-5D Visual Analog Scale (VAS) values, there was no available tool, so we used a custom-made function based on linear regression in patients with AD.

To conduct the linear regression, we used all studies identified in our SLR that included both EQ-5D VAS and EQ-5D index values for the same AD patient subgroups. We identified five studies that included these values [24–28]. The data points in these studies were run through a linear regression model using the least-squares method.

The following linear regression equation was used to convert EQ-5D VAS QoL scores to EQ-5D index values on a scale from 0 to 1:

$$y = 0.0136x - 0.1534$$

y: EQ-5D VAS QoL score, *x*: EQ-5D index QoL value.

Productivity Lost

Similarly, productivity lost was reported either as the number of days or hours lost during a certain period, or as a percentage lost in some cases. All values were unified to number of days lost annually per patient by using the Organisation for Economic Co-operation and Development average working hours per year value of 1726 and assuming eight working hours per day [29].

Multiple Regression

Several multiple linear regression models were developed using IBM SPSS statistics software version 25 to determine the main drivers for economic costs and QoL of AD. Economic costs in USD were used as the outcome of one model, while QoL in utility score was used as the outcome of the other model. Different numeric and nominal variables were used as the main predictors (e.g., male percentage, age, severity score). Only clinically and statistically significant models are presented in the results.

Compliance with Ethics Guidelines

This study is based on previously conducted research and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

The systematic search yielded 3400 records after de-duplicating hits from different databases plus 48 studies identified via other methods. A total of 233 studies were included in the analysis. Further details are available in Supplementary Fig. S2.

General Results

The majority (66.1%) of the included studies reported data from Europe and Central Asia, yet the most frequent country considered in studies was the USA (46 studies), followed by Germany (35 studies). High-income countries represented more than 85% of the included studies, while only one study reported from a low-income country. More than 90% of the studies were observational, while only 9 studies used economic models and 36 were systematic literature reviews.

Clinical Burden

Itching (also known as pruritis in some studies), depression, and anxiety were the most frequently reported impact parameters in the clinical burden domain (51, 49, and 42 mentions, respectively). Figure 1 shows the frequency of the different clinical burden domains of impact. Itching was the most commonly mentioned clinical impact due to AD. Based on the aggregated data points, the itching or pruritis prevalence in patients with AD ranged from 21% up to 100% [30–35].

Eight studies reported the median severity of itch due to AD based on a 0–10 numerical rating scale. The median values describing the severity of itch ranged from 4 to 9, with an average of 6 (where 10 represents the highest level of itch) [28, 36–42]. A similar range exists with mean values ranging from 3 to 9, with an average of 6, for studies using a VAS (also 0–10) [9, 43–49].

Eleven studies reported diagnosis of depression prevalence values among patients with AD [26, 30, 50–58]. The average of all prevalence values was 18%. Prevalence estimates ranged from 3% to 57%. These results were slightly different from the self-reported depression values, which ranged from 10% to 37%, with an average of 26% [59–62].

The prevalence of anxiety among patients with AD ranged from 1.2% to 64%. These values were reported by 11 studies with an average anxiety of 24.12%. According to Mizara et al. [63], 41% of patients had a Hospital Anxiety

Subgroup	Impact	Frequency of mentions, n
Psychological	Depression	49
	Anxiety	42
	Suicidal ideation	11
	Stress	9
	Other psychological impacts	8
Signs	Itch or pruritis	51
	Soreness/pain/tenderness	20
	Burning or heat or tingling sensation	6
	Skin tightness	2
	Skin sensitivity/sensitivity to sun	1
Symptoms	Dryness (xerosis)	13
	Redness (erythema)	11
	Bumps/blisters/papules/vesicles	6
	Thickening/lichenification	6
	Cracking/fissuring	5
	Edema/swelling	4
	Scaling/peeling	3
	Hardening/flaking	2
	Bleeding	2

Fig. 1 Frequency of mentioning different impacts related to clinical burden in the included studies

and Depression Score of at least 11, which indicates a definitive case of anxiety.

Humanistic Burden

Concerning the humanistic burden, AD was shown to decrease QoL by impacting different aspects of patients' lives. Among the included studies, the psychological impact was by far the most mentioned impact (78 times) causing loss in QoL, followed by sleep disturbance (55 times). The details of frequency of mentioning each aspect affecting patients' QoL is shown in Fig. 2.

Sleep disturbance was very common among studies discussing AD burden and included nocturnal awakening due to itch and difficulty in sleep induction [40, 64, 65]. According to the included studies, sleep disturbance results in using sleeping pills or feeling sleepy, unproductive, or lacking concentration during the day [52, 66]. Several studies reported sleep disturbance in more than 70% of patients with AD [34, 45, 65, 67], while others showed lower prevalence, as low as 4.18% [51]. One study used subgroups for sleep disturbances and reported that 38.4% of patients had no difficulties, 23.9% had mild difficulties, 28.2% had moderate difficulties, and 9.6% had severe difficulties in sleeping due to AD [68]. One study also showed that controlling AD resulted in better outcomes related to sleep disturbance: only 8.5% of patients with adequately controlled AD experienced sleep disturbances compared with 23.8% in patients with inadequately controlled AD [69].

QoL Score Burden

The average utility value for the AD general population was about 0.779 based on 71 studies. Patients with the lowest severity had the highest HRQoL (utility), represented by an average utility value of 0.873. HRQoL decreased gradually with increasing severity, with an average utility value of 0.548 for the most severe patients (Table 1).

Among 597 data point estimates for the QoL questionnaires, several questionnaires were used, including VAS (77), the 36-Item Short Form Health Survey (66), Patient-Oriented Eczema Measure (POEM) (46), EQ-5D (40), AD Burden Scale (36), and Skindex (33). Yet, DLQI and cDLQI questionnaires were the most used to assess the QoL for patients with AD (299 data points).

Impact	Frequency of mentions, n
Psychological	78
Sleep disturbance	55
Limitation in daily activity	33
Limitation in role: work	29
Limitation in social/leisure activities	25
Problems with interpersonal relationships	22
Limitation in role: school	21
Physical limitation	19
Problems with sexual functioning	15
Scratching	13
Bodily/physical discomfort	11
Lack of concentration	4
Suboptimal skin-related health perceptions/cognitions	4
Financial burden of buying special products	2

Fig. 2 Frequency of mentioning humanistic burden impacts in the included studies

Table 1 Utility values based on severity ranks

Severity rank	Number of studies reporting values	Average utility	Minimum utility	Maximum utility
Unstratified population	71	0.779	0.432	0.940
1	3	0.873	0.869	0.877
2	25	0.807	0.732	0.912
3	15	0.728	0.633	0.832
4	25	0.676	0.551	0.881
5	3	0.548	0.420	0.668

Multivariate Regression Model for Utility

According to the multivariate regression model (Table 2), male patients with AD had significantly lower utility compared with female patients. Age was not a statistically significant explanatory variable for utility. Conforming with previous findings (Table 1), severity was inversely proportional to utility value.

Economic Burden

Of the included studies, 70 provided data about costs and HCRU. Of those, 41 studies included (direct and indirect) cost data and 32 included HCRU data (e.g., number of outpatient visits). Twenty-eight studies included other economic data, of which the majority reported productivity loss.

Table 2 Multivariate regression model for utility of patients with AD

Parameter	Beta coefficient (β)	Standard error	95% Wald confidence interval		Hypothesis test		
			Lower	Upper	Wald chi-squared	Degrees of freedom (df)	Significance
(Intercept)	1.348	0.2433	0.871	1.825	30.675	1	0.000
Severity rank = 2	0.108	0.0256	0.058	0.158	17.746	1	0.000
Severity rank = 3	0.086	0.0504	−0.013	0.185	2.925	1	0.087
Severity rank = 4	0[a]						
Age, years	−0.005	0.0031	−0.011	0.001	2.626	1	0.105
% of males	−0.863	0.2772	−1.406	−0.319	9.686	1	0.002
Scale	0.001[b]	0.0006	0.001	0.003			

Dependent variable: quality of life
[a]Set to zero because this parameter is redundant
[b]Maximum-likelihood estimate

Healthcare Resource Utilization

Data collected for AD comprise a wide range of severity and diversity in HCRU, including outpatient visits, emergency department visits, and hospitalizations. Studies usually reported separate data for different severity groups.

Dermatologist visits ranged from 2.8 to 16.3 per year for the unstratified population, with an average of 8.6 [28, 59, 70–72]. Primary care/general practitioner visits averaged 16.5 per year [70, 73, 74], with this number varying significantly by severity, where it reached 20.44 healthcare provider visits per year in patients with moderate to severe AD [50]. Two studies reported the visits of patients with AD to medical specialists other than dermatology, which were allergy and internal medicine, with a rate of 0.2–0.4 visits per year, respectively [70, 72].

As severity increased, the frequency of emergency visits increased. However, for all severity ranks, studies reported a low rate of emergency department admissions. Considering unstratified patients with AD, studies reported a minimum of 0.05 visits per year and up to 1.22 visits per patient per year, with an average of 0.80 visits [50, 68, 71, 74, 75].

For patients with rank 2 severity, the average number of annual emergency department visits per patient was 0.5 [50, 68, 71, 73, 74]. The average was 0.92 visits for patients with rank 3 severity [68, 74] and 1.41 for rank 4 severity [50, 68, 71, 73, 74]. The average annual number of hospitalizations (for the unstratified population) ranged from 0.03 to 1.2 admissions [50, 71, 73, 75]. Patients with severity rank 4 had an average annual hospitalization rate of 0.75 per year [50, 68, 71, 73, 75]. On the other hand, those with severity rank 2 had an average annual hospitalization rate of 0.45 per year [68, 71, 73, 75].

Costs

There was significant heterogeneity between individual studies since the studies came from different countries and several income levels. The total cost of AD per patient was mentioned in eight studies, in which the annual average cost was estimated to be 5246 USD (2020), with a minimum of 769 USD and a maximum of 23,638 USD [72, 74, 76–81]. The average total cost calculated from the studies was less than the sum of average total direct and total indirect cost due to the heterogeneity in sources and calculation methods. Nine studies reported total direct costs with an annual average cost of 4411 USD [48, 72, 76, 82–87]. The total indirect cost per patient was reported in three studies with an average cost of 9068 USD per year [72, 76, 88]. Cost details are presented in Table 3.

Some studies reported economic data stratified by different factors, most commonly by severity (24 studies), followed by treatment groups (12 studies) and age (9 studies). The exact studies and strata are reported in Supplementary Table S2.

Productivity Lost

Several studies mentioned the economic burden incurred by AD due to productivity lost, which was usually quantified by the number of days of absenteeism and/or presenteeism. Among 28 studies reporting numbers or percentages of workdays lost due to AD as presenteeism or absenteeism, 20 reported absenteeism values separately, 13 reported presenteeism separately,

Table 3 Average annual cost per patient with AD (unweighted)

Type of economic burden (direct/indirect)	Number of studies reporting the cost	Number of patients in the studies	Minimum reported cost (2020 USD)	Average cost (2020 USD)	Maximum reported cost (2020 USD)
Total direct cost	9	119,750	940	4411	11,536
Total indirect cost	3	218	1289	9068	15,650

and 14 reported both absenteeism and presenteeism values.

Productivity is significantly affected by AD, as seen by a total of 68.8 days lost annually due to absenteeism and presenteeism combined (for the unstratified population). The presenteeism (54 days lost) [42, 59–61, 72, 73, 78, 83, 89–91] effect was dominant, being more than three times the days lost due to absenteeism (14.8 days lost) [42, 59–61, 65, 72, 73, 78, 83, 88–93]. Productivity lost in days differed significantly among severity ranks, with patients with severity rank 5 losing on average 26.5 days due to absenteeism and 92.5 days due to presenteeism, compared with patients with rank 1, who lost an average of 2.5 days due to absenteeism and 13.6 days due to presenteeism [78, 94]. Table 4 presents the average number of days lost due to absenteeism and presenteeism based on the severity rank.

DISCUSSION

The highly prevalent chronic inflammatory skin disease AD affects adults and adolescents, with a significant DALY burden [1]. However, until recently, AD was generally considered to be merely a skin disorder [95]. Many efforts have been made to quantify different aspects of the burden of AD. We aimed to aggregate the findings from different studies to provide a holistic view of AD burden from the humanistic, economic, and clinical perspectives for adult and adolescent patients. Furthermore, due to the abundance of studies evaluating each burden element, we were able to stratify the impact based on additional factors, such as severity.

Table 4 Average number of days lost per year due to absenteeism and presenteeism, by severity rank

Severity rank	Absenteeism only	Presenteeism only	Total
Unstratified population	14.8	54.0	68.8
1	2.5	13.6	16.1
2	14.0	58.5	72.5
3	23.3	78.5	101.8
4	24.0	95.5	119.4
5	26.5	92.5	119.0

To date, there is no cure for AD [96]. However, based on these results that show a solid correlation between severity and HRQoL, as well as productivity lost, maintaining patients with mild disease severity could offset most of the burden. This study should be considered as a first step in mitigating the burden of AD by providing an overview of the scale and factors of AD burden. The next step to decrease AD burden should be to research further into specific policy actions that could improve the prognosis of patients with AD. This research should be validated from a local perspective to ensure its eligibility within the healthcare system structure and from the cultural perspective.

The burden of AD might be underestimated in low- and middle-income countries because, despite the abundance of literature on the topic, most of the literature came from higher-income countries; low- and middle-income countries were not equivalently represented in the literature. The global burden of disease study found a positive correlation between disease burden and gross domestic product [1]; however, this might be due to insufficient data and underreporting of AD in lower- and middle-income countries.

As expected, itching was the most commonly mentioned symptom in the literature for patients with AD, in some cases being reported to affect 100% of patients. This symptom was followed by depression and anxiety, which highlights the significance of the psychological illness impact on patients with AD, which was further confirmed by the humanistic burden data, where again, psychological illness ranked number one in terms of frequency of mentions in the literature. Sleep disturbance followed psychological illness in the ranking within the humanistic burden, which is not unexpected since it is linked to nocturnal awakening due to itch [64]. Although sleep disturbance might not be an issue if it is a one-night problem, the impact is amplified when the confounding

factor is a chronic disease, and the majority of patients with AD do experience sleep disturbance. Sleep disturbance can lead to a cascade of implications, such as the use of sleeping pills, and usually causes a lack of concentration and lethargy [64, 66].

One of the main consequences of sleep disturbance is productivity loss due to lack of concentration, and lethargy, which might explain the significantly higher presenteeism compared with absenteeism. The productivity lost for the unstratified population by severity made up about one-third of the year, while for the most severe cases, the total productivity lost even exceeded half of the year.

Looking at the HRQoL, the variability of utility lost between different severity groups was significantly wide, which was further confirmed when we developed a multiple regression model that included severity, age, and sex as independent variables.

Our results concerning humanistic burden are concordant with a recent study in Europe assessing the AD burden of illness in adults [61]. It also states that anxiety, depression, sleep disorders, and overall and general impairment create a significant burden for patients with AD compared with controls. Another study by Reed et al. also confirms our findings of the significant losses in QoL and school or work absenteeism burden due to AD [97].

Drucker et al. estimated a similar total annual cost per patient in the USA in 2013 [75], ranging from 3302 to 4463 USD, compared with our estimate of 4411 USD. However, our estimate is not confined only to the USA. The similarity of these values is probably due to the underreporting of the burden in low- and middle-income countries, which might have decreased the average cost if their data were available, as these countries usually have lower unit costs owing to their relatively low gross domestic product.

Because of the diversity of the included studies, each had a different methodology and perspective; therefore, for some calculations, the values from two or more studies could not be used for summary statistics. However, we grouped similar methodological articles for each part of the burden and created summary statistics for specific subgroups. For the same reason, all summary statistics were calculated as nonweighted average values as it was not feasible to calculate the statistics based on the number of patients in each study due to the diversity of studies. Since severity was not measured in the same way in all included studies, we used the severity ranking approach. Although this approach may not provide the most accurate severity estimates, we assume that it is sufficient to provide useful insights about the burden. As costs from different studies were converted to USD and adjusted for inflation, the aggregated results should be interpreted with caution, as the purchasing power parity and treatment protocols, as well as the variance between drugs and medical services in different countries, might have significant effects. The regression was performed without considering the weights of patient numbers because of the difficulties in extracting the number of patients for each subgroup of patients as they usually overlapped.

CONCLUSIONS

The burden of AD is significant due to its high prevalence as well as the magnitude of its impact. While the disease is incurable, reducing the severity of the disease and modifying the prognosis of patients could significantly reduce the burden.

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REVIEW

Humanistic and Economic Burden of Atopic Dermatitis for Adults and Adolescents in the Middle East and Africa Region

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic skin disease that poses a significant burden on both patients and the society. AD causes the highest loss in disability-adjusted life years compared with other skin diseases. This study aimed to estimate the economic and humanistic burden of AD in adults and adolescents in seven countries in the Middle East and Africa region (Egypt, Lebanon, Saudi Arabia, Kuwait, Algeria, South Africa, and United Arab Emirates).

Methods: We conducted a literature review to identify country-specific data on this disease. Subsequently, meetings were organized with experts from each country to complete the missing data. The data were aggregated and calculation models were created to estimate the value of the humanistic and economic burden

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of the disease in each country. Finally, we conducted meetings with local experts to validate the results, and the necessary adjustments were made.

Results: On average, a patient with AD loses 0.19 quality-adjusted life years (QALYs) annually owing to this disease. The average annual healthcare cost per patient is highest in the United Arab Emirates, with an estimated value of US $3569 and a population-level indirect cost of US $112.5 million. The included countries allocated a range of 0.20–0.77% of their healthcare expenditure to AD-related healthcare services and technologies. The indirect cost of AD represents approximately 67% of the total disease cost and, on average, approximately 0.043% (range 0.022–0.059%) of the gross domestic product (GDP) of each country.

Conclusion: Although the humanistic and economic burdens differ from country to country, AD carries a significant socioeconomic burden in all countries. The quality of life is severely affected by the disease. If AD is controlled, the costs, especially indirect costs, could decrease and the disease burden could be alleviated significantly.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis is a chronic condition characterized by inflamed and itchy skin. The prevalence and symptoms of atopic dermatitis are observed to increase in dry weather. Owing to its high prevalence in children, the majority of studies on atopic dermatitis are in children. Although it is also prevalent in adults and adolescents, its burden on adults has not been sufficiently studied, especially in Africa and the Middle East. This study quantified the burden of atopic dermatitis in adults and adolescents in seven countries in the Middle East and Africa. We estimated the economic and humanistic burden of this disease. We conducted a literature review and expert interviews to determine the effects on patients and caregivers. We created mathematical models to calculate the disease burden in each country, and local experts in each country validated the data. The study results showed that atopic dermatitis significantly affects the quality of life of patients. The direct medical costs of treatment in each country were calculated. The management of

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atopic dermatitis consumes around 0.20–0.77% of the healthcare expenditure in a country. The indirect cost of atopic dermatitis represents 0.022–0.059% of the gross domestic product (GDP) of a country. The country-specific burden data are essential to guide decision-makers in arriving at evidence-based decisions and efficiently allocating available resources. This study focused on the significant indirect economic burden of the disease, which can sometimes be underestimated because the disease is not fatal.

Keywords: Atopic dermatitis; Africa; Disease burden; Economic burden; Eczema; Humanistic burden; Middle East; Quality of life

Key Summary Points
The burden of atopic dermatitis has not been sufficiently quantified in Africa and the Middle East.
The quality of life of patients and caregivers is severely affected by atopic dermatitis.
Atopic dermatitis carries a significant socioeconomic burden worldwide.
There is an opportunity to decrease the disease burden through proper management.
By controlling diseases, the costs and quality of life loss burden can be alleviated significantly.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic skin disease that significantly decreases the quality of life of patients [1]. It may also lead to economic losses for patients and societies, especially in a severe state [2]. AD is occasionally mistaken for a pediatric disease because it is very common in children; however, recent studies have shown that AD is also common in adults, with a prevalence ranging from 2.1% to 4.9% [3]. This disease creates a significant humanistic and economic burden for individual patients and society [4, 5]. The Global Burden of Disease study estimated that AD has the highest burden of disability-adjusted life years (DALYs) among skin diseases, exceeding that of psoriasis (75% higher), urticaria (82% higher), and scabies (more than 100% higher) [6]. Globally, the age-standardized rate of disability-adjusted life years is higher for AD than for other serious diseases, such as liver cirrhosis and alcohol-associated chronic liver diseases [6].

The treatments for AD include a wide range of topical and systemic agents, targeted therapies, and phototherapies. The treatment costs vary among these options, from inexpensive topical anti-inflammatory agents and emollients to expensive targeted therapies [7]. In addition to direct healthcare costs, AD also implies a hidden indirect cost that represents a considerable proportion of the total cost [8].

The prevalence of AD and its manifestations are affected by the climate. The disease tends to manifest more in dry weather [9, 10]; therefore, the burden may vary according to the climate of each country. The burden of AD in the Middle East and Africa has been discussed in a recent literature review [11], and other reviews have estimated its prevalence or burden in specific cities [12, 13]; however, to our knowledge, this is the first study to quantify the burden of the disease in adults and adolescents in specific countries in the region. Country-specific burden data are essential to allow decision-makers to make evidence-based decisions and efficiently allocate the available resources.

This study aimed to estimate the economic and humanistic burden of AD in adults and

adolescents in seven countries in the Middle East and Africa region: Algeria, Egypt, Kuwait, Lebanon, Saudi Arabia (KSA), South Africa, and the United Arab Emirates (UAE).

METHODS

Primary and secondary data were used to estimate the disease burden. We conducted a literature search and expert interviews to obtain and validate the data on humanistic and economic burdens in the seven selected countries. Additionally, calculation models were created using Microsoft Excel to quantify the burden in each country. We used a bottom-up approach to estimate the humanistic and economic burdens. The values of quality-adjusted life years (QALYs) lost, as well as the healthcare costs and indirect costs incurred by an average patient with AD, were multiplied by the number of patients with AD in a country to estimate the total burden. In general, this study had a conservative approach: if we could not find an accurate estimate of an input, its lower estimate was used; therefore, the actual burden is safely more than the estimate we have provided.

Prevalence

For the bottom-up calculation, the data on the number of adults and adolescents with AD in each country were required. These prevalence data should be stratified by age group because the quality of life and prevalence differ significantly among age groups. We used prevalence data estimates for the seven countries from the Global Burden of Disease study [14]. The 2019 prevalence data (latest reports) are presented in Table 1. The prevalence details by age and sex are shown in Table S1.

Humanistic Burden

To estimate the humanistic burden of AD in the seven selected countries, we multiplied the number of patients in each country by the average loss in quality of life annually (the value of utility lost per patient in 1 year).

Table 1 Patients with AD aged 10–74 years in the selected countries. Source: Global Burden of Disease Results Tool (Global Health Data Exchange) [34]

Country	2019 prevalence of AD, n		
	Male patients	Female patients	Total
Algeria	156,053	209,150	365,204
Egypt	235,771	309,446	545,217
Kuwait	18,836	22,856	41,691
Lebanon	18,497	25,663	44,161
Saudi Arabia	175,133	167,752	342,885
South Africa	157,835	196,936	354,771
United Arab Emirates	56,623	28,262	84,885

AD atopic dermatitis

There were no country-level data regarding the values of the annual utilities lost owing to AD; therefore, we opted to use data from international studies to calculate the age-standardized QALYs lost. We specifically searched for studies reporting the quality of life subgrouped by age because the utility loss differs among different age groups.

Beikert et al. [15] reported the quality-of-life values for patients with AD sub-grouped by age as EuroQoL 5-dimension (EQ-5D) visual analog scale values. To use these data to estimate the utility loss per age group, we converted the data into 0–1 utility values. There was no ready-made tool for this conversion; therefore, a regression model was built on the basis of five studies identified in the literature [16–20]. Each of these studies included EQ-5D index utility values and EQ-5D visual analog scale results for the same group of patients. We used these values to create a regression model and converted the EQ-5D visual analog scale values to EQ-5D index utility values.

Beikert et al. reported only values for patients aged ≥ 18 years; therefore, we used the data from another study (Ezzedine et al.) [21] to determine the quality of life for patients aged 10–18 years. Ezzedine et al. reported the utility

values for patients aged 12–14 and 15–17 years. These values were used as proxies for the quality of life for those in the 10–14 and 15–19 age groups, respectively, to match the prevalence age structure grouping. In the study by Ezzedine et al., the quality-of-life values were reported on the basis of the children and adult versions of the Dermatology Life Quality Index (DLQI) questionnaire results, which were converted into EQ-5D index utility values through a specialized online tool [22].

After collecting the utility values for all patient age groups, we calculated the utility loss from the general population (the utility each patient with AD loses owing to the disease compared with the utility of the general population). The utility of the general population for each age group was reported by Janssen et al. [23] in 20 countries worldwide. We calculated the average utility for all countries, and assumed that this would be the baseline utility for each age group. The study reported values for those aged 18–75 years. We assumed that the patients in the 10–15 and 15–19 age groups would have the same quality of life as the 18–24 age subgroup.

Finally, to calculate the utility loss owing to AD, the utility value for a patient with AD in each subgroup was subtracted from that for the general population in the same subgroup. The humanistic burden in each country was calculated by multiplying the number of patients in each age group by the average utility lost for the same age group over 1 year. The product represents the QALYs lost per country per year owing to AD. The age-standardized utility loss per patient for each country was calculated by dividing the total QALYs lost by the number of patients with AD in each country. This value was calculated to allow comparability between countries.

To calculate the monetary value of QALYs lost owing to AD, the annual QALYs lost in the previous step were multiplied by the gross domestic product (GDP) per capita for each country in 2019 USD. To allow for comparability between countries, the total monetary value of QALYs lost was divided by each country's GDP, and countries were compared by the monetary value of QALYs lost as a percentage of GDP. We obtained GDP and GDP per capita values from the 2018 World Health Organization Global Health Expenditure database [24].

Economic Burden: Healthcare Costs

The healthcare costs items included outpatient visits, hospitalization, topical treatments, systematic treatments, targeted therapy, and phototherapy sessions. As the economic data are not transferable across countries, we collected the local data on the costs from each country. We conducted a series of structured interviews with experts from each country to estimate the healthcare costs of AD. The questionnaire used in the interview was based on a scoping review conducted to identify the relevant cost components related to the disease. This questionnaire was validated by a healthcare professional who recommended that the questionnaire should be stratified by severity levels (mild, moderate, and severe) because each level requires different interventions and, therefore, has different costs.

We conducted interviews with two or three healthcare professionals from each country. For each country, at least two experts were interviewed. If the results of the two estimates differed significantly (more than double the average), a third interview with a different expert was conducted. Among the three results, the lowest two results were chosen as per the conservative approach of the study.

The data collected during the interviews included the severity distribution among patients and the details of healthcare costs, such as healthcare resource utilization, outpatient visits, length of hospital stay, lab tests, and topical and systemic treatments for each severity level.

The public unit costs of treatments or services for patients with AD were collected for each country from online official price lists, online pharmacy prices, and hospital prices or expert interviews, if all the previous data were unavailable. The questionnaire template and details of each domain can be found in Tables S2 and S3. To allow for comparability between countries, the cost values were

converted to 2019 USD using the annual average exchange rate from the World Bank database [25]. The values of healthcare costs for AD as a percentage of the total healthcare expenditure were calculated for each country to assess the relative healthcare cost burden. We obtained data on healthcare expenditures from the 2018 World Health Organization Global Health Expenditure database [24].

The questionnaire was sent to each healthcare professional to understand its structure, and an online structured 2-h interview was conducted with each healthcare professional to complete the questionnaire. The interviewers completed the questionnaires on the basis of the experts' answers. A total of 17 clinical experts were interviewed. These experts were selected on the basis of a convenience sampling technique in each country, choosing accessible healthcare professionals who have experience in dermatology.

The questionnaires aimed to provide data on the annual average cost burden of AD per patient per country. To estimate the total healthcare cost per country, we multiplied the number of patients in each country by the average cost per patient (obtained from the questionnaire).

Not all patients with AD are diagnosed, and not all patients are treated [3]. The untreated population will, of course, incur no healthcare costs. Hanifin et al. estimated the percentage of AD cases diagnosed by a physician to be 37.1% [26]. Accordingly, the healthcare costs in our study were multiplied by 37.1% to adjust for the proportion of diagnosed and treated patients.

Economic Burden: Indirect Costs

On the basis of the literature search conducted, the indirect costs of AD are mainly related to productivity loss owing to absenteeism and presenteeism of patients and their caregivers. Absenteeism was defined as the number of days the patient was absent from work or school, and presenteeism was defined as the number of days the patient was at work or school, but was not productive [27].

The average annual presenteeism and absenteeism values for each patient with AD were calculated on the basis of a literature search of several studies that included numerical data on presenteeism and absenteeism owing to AD. A list of studies reporting absenteeism and presenteeism data is presented in Table S4. Few studies mentioned data on absenteeism for caregivers; most studies that included these data focused only on children. Therefore, because our study adopted a conservative approach and included adults and adolescents, the caregiver burden was excluded from our calculations. The reported presenteeism and absenteeism values were estimated on the basis of the weighted average of the AD severity.

The following example shows how presenteeism and absenteeism values were estimated from each study:

> If patients with AD of mild severity represent 50% of the study population, and are absent for 5 days on average owing to AD, patients with moderate AD represent 35% and are absent for 15 days, and patients with severe AD represent 15% and are absent for 25 days, then the average absenteeism value would be calculated as $50\% \times 5 + 35\% \times 15 + 15\% \times 25 = 11.5$ days of absenteeism annually for an average patient with AD.

The average productivity lost by patients in the literature was adapted to local settings, considering the prevalence of working age, employment rate, sex, and labor force participation rate (LFPR) [28–30]. These inputs were used to calculate the AD-related indirect costs owing to absenteeism and presenteeism.

To calculate the value of indirect costs for a whole country population, the approach was to multiply the number of patients in the working age group (age, 15–65 years) by the cost of 1 day of presenteeism or absenteeism, and the annual number of days lost. The cost of 1 day was calculated on the basis of the average salary in the country and number of working days per year. Simultaneously, the number of working patients was adjusted to the LFPR and unemployment rate by sex.

The following equation was created and used to calculate the productivity lost:

((LFPR male × (1 − unemployment rate) × prevalence male) + (LFPR female × (1 − unemployment rate) × prevalence female)) × (absenteeism OR presenteeism value) × Average daily salary.

Validation Meetings

Our results are based on several sources. Local experts from each country validated the extracted and synthesized data. We conducted meetings with experts (payers and healthcare professionals) in the field to validate our results regarding the humanistic and economic burden in light of their local settings and culture. The healthcare professionals involved in the initial data collection did not contribute to validation.

Two research team members managed and coordinated each validation meeting (principal researcher and senior researcher). The meetings were conducted online with local experts who provided feedback about the results, recommended some changes, and provided better or more updated references for some data points. The meetings were recorded and transcribed, and all the key points of the validators were addressed. The research findings and calculations were updated after the validation meetings, and the estimates were adjusted on the basis of recommendations.

An example of the changes recommended by validators and applied to the results is using the unemployment rate reported by the Department of Statistics in South Africa [28] rather than another older estimate. Additionally, in South Africa experts recommended adding the average dispensing fee to drug prices instead of using the single exit price. In Lebanon, experts advised on using the average salary provided by the Salary Explorer website [31]. A summary of the results of the validation meetings and modifications can be found in Table S5.

Compliance with Ethics Guidelines This study is based on previously conducted research and does not include any new studies with human participants or animals performed by any of the authors.

RESULTS

Humanistic Burden

The humanistic burden of AD is expressed as the utility loss per age group. The estimated utility value of an average patient with AD ranges from 0.54 to 0.77 (adjusted from Beikert et al. [15] and Ezzedine et al. [21]). Compared with the average population, the patients with AD are estimated to lose between 0.09 and 0.28 QALYs annually owing to AD. The details of the lost utility per patient are presented in Table 2.

At the country level, the aggregated QALY loss is higher in countries with larger populations. Egypt suffered the highest QALY loss, and Kuwait had the lowest QALY loss owing to AD. The aggregated AD humanistic burden is approximately 334,000 QALYs lost annually in the seven countries included in this study. The age-standardized utility loss per patient per country ranged from 0.185 to 0.189. The

Table 2 Estimated annual utility lost per patient with AD, by age group

Age range, years	Average non-patient utility[a]	Average patient utility[b]	Average utility lost per patient
10–14	0.93	0.76	0.17
15–19	0.93	0.70	0.23
20–24	0.93	0.77	0.15
25–34	0.92	0.73	0.18
35–44	0.90	0.71	0.19
45–54	0.86	0.68	0.18
55–64	0.82	0.54	0.28
65–74	0.80	0.71	0.09
≥ 75	0.72	0.61	0.11

AD atopic dermatitis

[a]Values adapted from Janssen et al. [23]

[b]Values adapted from Beikert et al. [15] and Ezzedine et al. [21]

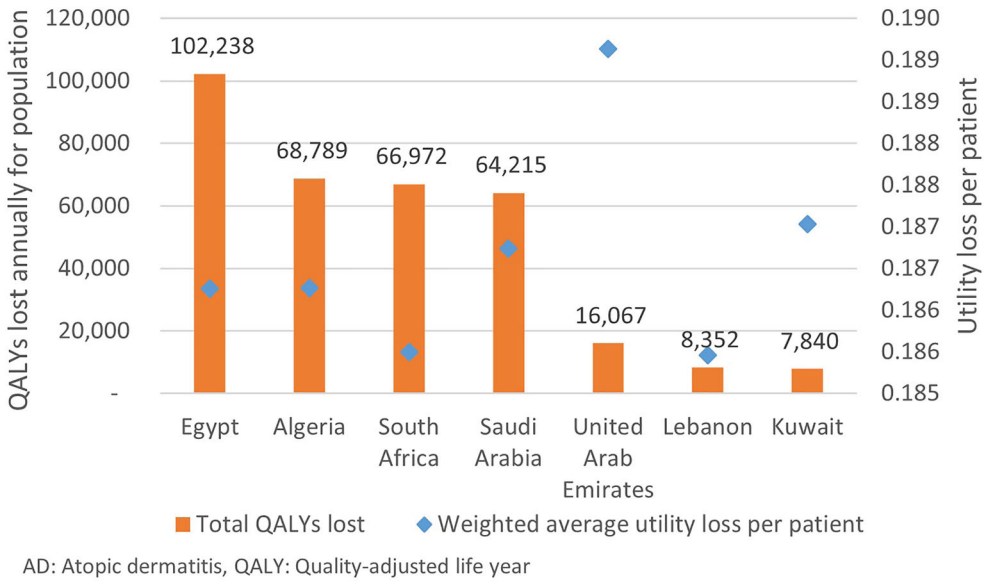

Fig. 1 Annual lost QALYs per country and utility loss per patient owing to AD. *AD* atopic dermatitis, *QALY* quality-adjusted life year

average utility loss per patient for the seven countries was estimated at 0.187. The details of humanistic burden including QALYs lost per country and utility lost per patient are shown in Fig. 1.

Healthcare Costs

The cost of AD per patient largely depends on the economic status and the prices of healthcare services of each country. The costs for each severity level were determined, and the weighted average was calculated to provide a single estimate for an average patient. The average annual healthcare cost was calculated for each country; the healthcare cost domains are detailed in Table S3.

In Algeria, the annual cost per patient is US $312. This cost is the lowest among the seven countries. The results showed that the UAE and Kuwait had a remarkably high average cost per patient compared with other countries in the region: US $3569 and US $2880 per patient, respectively. In most of the questionnaires conducted, the use of targeted therapies, with prices much higher than those of other topical or systemic interventions, was considered one of the main cost drivers. In countries where targeted therapies are more frequently used, the average cost per patient tends to be much higher than that in countries where targeted therapies are not commonly prescribed.

For country-level costs, the UAE also had the highest annual cost at US $112.5 million, followed by Saudi Arabia and Egypt with US $99.5 million and US $95.5 million, respectively. The lowest annual cost was in Lebanon at US $13.6

Table 3 Average annual healthcare cost for AD per patient and per country

Country	Average annual cost per patient	Annual cost per country (million)
Algeria	312	42.8
Egypt	469	95.5
Kuwait	2880	44.8
Lebanon	817	13.6
Saudi Arabia	780	99.5
South Africa	449	60.1
United Arab Emirates	3569	112.5

All costs are in 2019 USD
AD atopic dermatitis

million. The total healthcare costs of the seven countries combined were estimated at more than US $460 million. The annual healthcare cost estimates are presented in Table 3.

Using the absolute healthcare cost values for these countries, which do not share the same income level or healthcare expenditure, makes it difficult to compare the burdens of these countries. Therefore, we calculated the healthcare cost burden of AD as the ratio of the annual healthcare expenditure in each country. Egypt showed the highest cost for AD per healthcare expenditure at 0.77%, and South Africa and Saudi Arabia showed the lowest, at only 0.2%. On average, the healthcare cost of AD accounts for approximately 0.4% of the total health expenditure in these countries. The details are shown in Fig. 2.

Indirect Costs

The literature search showed an annual productivity loss of 6.1 days of absenteeism and 22.9 days of presenteeism owing to AD for an average patient (average of all severity-level patients). This means that, on average, each patient with AD loses approximately 28.9 days of productivity annually because of the disease.

Compared with the other countries included in this study, Saudi Arabia had the highest annual loss in indirect costs owing to AD (US $364 million), followed by the UAE (US $228 million) and South Africa (US $152 million). Kuwait, Egypt, Algeria, and Lebanon had much lower values, ranging from US $33 million in Lebanon (the lowest) to US $62 million in Kuwait. To show the relative effect of the disease on each country, these values were divided by the respective GDP of each country. The indirect cost of AD as a percentage of GDP was the highest in Lebanon (0.061%) and lowest in Egypt (0.022%). The average indirect cost, as a percentage of the national GDP for the seven countries, was 0.041%. The details of indirect costs are shown in Fig. 3.

Total Burden

The total burden of AD comprises the total economic burden (healthcare and indirect costs) and the monetary value of the QALYs lost owing to the disease.

The economic burden of countries owing to AD was calculated as the sum of healthcare and indirect costs of each country. The total economic burden of AD in Saudi Arabia was

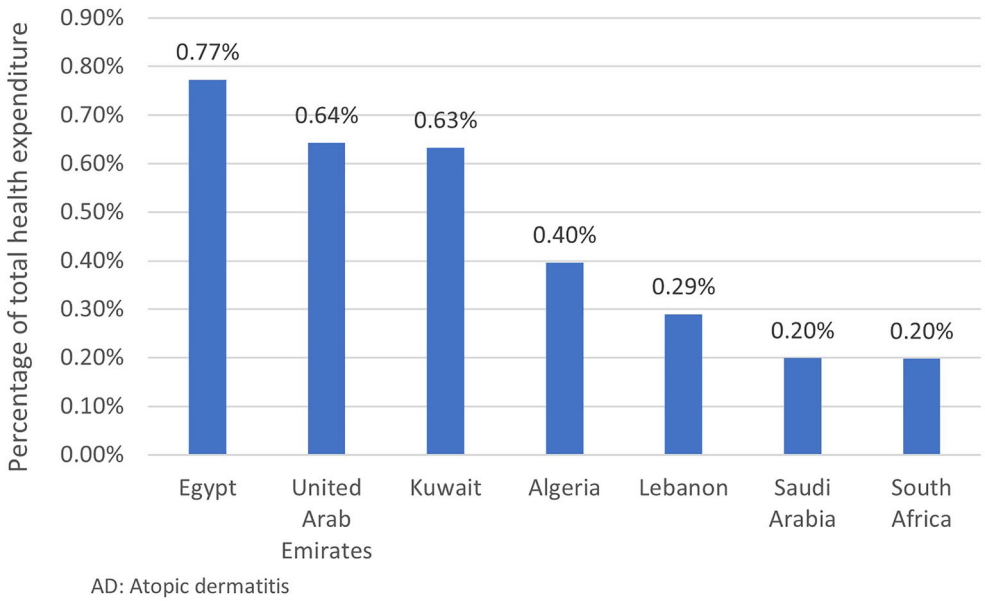

Fig. 2 Annual cost of AD as a percentage of total health expenditure. *AD* atopic dermatitis

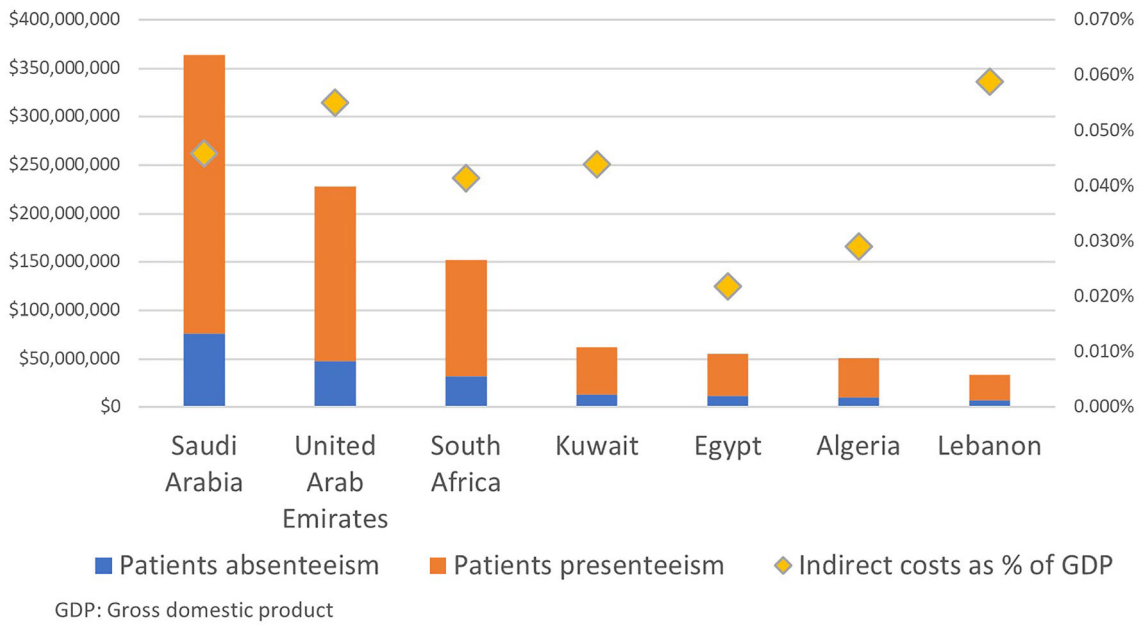

Fig. 3 Absenteeism, presenteeism, and total indirect costs as absolute values, and total indirect costs as a percentage of national GDP. *GDP* gross domestic product. All costs are in 2019 USD

observed to be the highest, at US $463 million annually. The aggregated economic burden of the seven countries exceeds US $1.4 billion annually.

Indirect costs represented a significant portion of the total economic burden, ranging from 37% in Egypt to 79% in Saudi Arabia. On average, the indirect costs represented 67% of the total AD cost.

The monetary value of QALYs lost was calculated as the product of QALYs lost and GDP per capita for each country. The QALYs lost were translated into a monetary loss ranging from US $66.9 million in Lebanon to approximately US $1.5 billion in Saudi Arabia.

Table 4 presents a summary of the healthcare and indirect costs and their contribution to the total economic burden as a percentage as well as the monetary value of the QALYs lost. The sum of these values (total economic burden and monetary value of QALYs lost) provides an estimate of the total burden of AD in adults and adolescents in each country.

As the seven countries differ in their economic status and size, the relative burden of the disease was calculated by dividing the estimated values for each country by its GDP. The AD healthcare costs ranged from 0.013% to 0.038% of the GDP in these countries. The indirect costs ranged from 0.022% to 0.061%. The total economic burden ranges from 0.046% to 0.085%. The loss was much higher when including the humanistic burden in the calculation because each QALY lost owing to the disease was translated into monetary losses. The estimated monetary value of the QALYs lost ranged from 0.104% to 0.191% of each country's GDP. On the basis of this, the total burden of the disease ranges from 0.164% to 0.265% of the national GDP in these countries. The monetary value of QALYs lost represented a considerable share of this total burden, with the humanistic burden representing approximately 2.4 times the total economic burden in all countries. Details of the relative burden of AD are presented in Table 5.

DISCUSSION

Our results show that AD in adults and adolescents causes a significant burden in all seven countries that were studied in the Middle East and Africa region. These results were obtained

Table 4 Total annual monetary burden of AD as sum of economic burden and monetary value of QALYs lost (humanistic burden)

Country	Economic burden			Monetary Value of QALYs lost	Total burden
	Healthcare costs[a]	Indirect costs[a]	Total economic burden[b]		
Algeria	42.8 (53)	37.9 (47)	80.7	285.7	366.4
Egypt	95.5 (63)	54.9 (37)	150.4	259.4	409.8
Kuwait	44.8 (42)	61.7 (58)	106.5	266.5	373.0
Lebanon	13.6 (29)	33.3 (71)	46.9	66.9	113.9
Saudi Arabia	99.5 (21)	363.7 (79)	463.2	1498.6	1961.8
South Africa	60.1 (28)	152.1 (72)	212.2	426.8	639.0
United Arab Emirates	112.5 (33)	228.0 (67)	340.5	704.4	1044.9

All costs are shown in 2019 USD per million
AD atopic dermatitis, *QALY* quality-adjusted life year
[a]USD (% of total economic burden)
[b]The sum of healthcare costs and indirect costs

Table 5 AD healthcare costs, indirect costs, and total economic burden as a percentage of national GDP

Country	Cost as % of GDP				
	Economic burden				
	Healthcare cost	Indirect cost	Total economic burden[a]	Monetary Value of QALYs lost	Total burden
Algeria	0.022	0.024	0.046	0.163	0.209
Egypt	0.038	0.022	0.060	0.104	0.164
Kuwait	0.032	0.044	0.076	0.189	0.265
Lebanon	0.025	0.061	0.085	0.122	0.207
Saudi Arabia	0.013	0.046	0.059	0.191	0.249
South Africa	0.016	0.041	0.058	0.116	0.174
United Arab Emirates	0.027	0.054	0.081	0.167	0.247

AD atopic dermatitis, *GDP* gross domestic product, *QALY* quality-adjusted life year
[a]The sum of healthcare costs and indirect costs

despite the heterogeneous age structures, income levels, and population sizes in these countries. The aggregated results show that, on average, patients with AD lose 19% of their health-related quality of life owing to their disease. This value is comparable to the utility decrements of more severe conditions, such as kidney transplantation [32]. The value of the total QALYs lost per country was associated with population size, with Egypt (most

populous among the included countries) experiencing the greatest loss and Kuwait (least populous) experiencing the lowest loss.

The average healthcare cost per patient was highest in higher-income countries (the UAE and Kuwait). Medical interventions in these countries seem to be relatively more expensive, resulting in higher costs per patient. On the basis of the questionnaire results, more advanced treatments, such as targeted therapies and phototherapy, are more common in higher-income countries. The healthcare cost of AD represents 0.20–0.77% of the total healthcare expenditure in the countries studied here, with an unweighted average of 0.4%, which is comparable to other significant contributors to healthcare expenditure. For example, in Germany in 2019, screening programs represented 0.6% of the total healthcare expenditure and maternity services represented 0.3% [33]. For country-level healthcare costs, the calculated values were affected by the population size and income level. The UAE had the highest burden owing to its high GDP per capita, followed by Saudi Arabia, which has a lower GDP per capita, but a larger population, and Egypt, which has the largest population, but a lower GDP per capita.

The indirect costs are also related to income level and population size. Among the countries studied, Saudi Arabia had the highest indirect costs related to AD. This is probably owing to the fact that among the seven countries, Saudi Arabia is the only country that has a combination of a relatively large population and a high per capita GDP. Egypt, for example, has the largest population, but has a low average annual salary; therefore, the indirect costs were not high.

Presenteeism contributed more than absenteeism to indirect costs. The indirect costs represent a significantly greater portion of the total burden than healthcare costs in most countries, accounting for up to 79% of the total economic burden in Saudi Arabia. Only Algeria and Egypt had lower indirect costs than healthcare costs. However, the indirect costs of AD pose a substantial societal burden, representing an average of 61% of the economic burden.

The total burden was significantly affected when humanistic burden was translated into an economic figure. In the UAE and Egypt, the monetary value of QALYs lost exceeded three times the aggregated healthcare and indirect costs. The humanistic burden represented 2.4 times the total economic burden on average for all countries. This shows that AD is associated with a significant hidden burden that may be considered much higher than the direct, tangible burden.

Limitations

Owing to the scarcity of local data for the included countries, the age-standardized QALYs lost and lost productivity were calculated by adjusting the international data to local demographics. This approach may not have captured the exact local burden and, more importantly, may have ignored, to some extent, the differences in disease severity across countries. The estimated burden is probably an underestimation owing to the prevalence estimates from the Global Burden of Disease study, which are significantly lower than those of most other studies reporting the prevalence of AD. However, owing to the lack of age-stratified prevalence data in other studies, we used the best available estimates.

When we calculated the total economic burden, we assumed that the healthcare costs of AD were equal to the total direct costs, excluding other cost components that may contribute to direct costs, such as direct nonmedical costs.

On the basis of the experts' opinions, other factors were not accounted for in the study, such as the effect on mental health, use of antidepressants, side effects of treatments, effect on career choice, and psychological effect on caregivers. However, these are partially accounted for in humanistic burden estimates.

Another factor confirming that our economic burden estimate for AD should be considered as a minimum estimate is the extra expense incurred by patients owing to the disease (e.g., personal care products and other informal costs). These expenses are usually

difficult to calculate, but negatively affect a patient's financial state.

For these reasons, further local studies are recommended to obtain a more accurate estimate of the burden of AD that considers the local healthcare system and various cultural aspects, specifically in terms of productivity loss and quality of life burden.

CONCLUSION

AD carries a considerable burden, mainly owing to the poor quality of life and significant productivity loss in patients. However, unlike diseases with high mortality, resource allocation is less prioritized for AD because the disease mainly affects the quality of life rather than the life years of the patients.

This study explored the humanistic and economic burdens of AD in adult and adolescent patients, combining the estimates of the minimum economic burden expected from healthcare and indirect costs related to the disease, which is significant in the geographic regions of the Middle East and Africa, as elsewhere. More evidence-based studies in the Middle East and Africa are needed for lobbying governments to allocate resources to help ease the burden of the disease. In addition, several interventions can be studied to alleviate this burden in these countries. These interventions should aim to optimize the treatment of AD to decrease the burden.

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Data Availability. All data generated or analysed during this study are included in this published article/as supplementary information files.

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The humanistic and economic burden of atopic dermatitis among adults and adolescents in Saudi Arabia

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ABSTRACT

Aims: Atopic dermatitis (AD) is a chronic skin disease that creates a significant burden to patients and society. There is scarcity in local data about the burden of AD in the Kingdom of Saudi Arabia (KSA). We aimed to fill in this gap and quantify the humanistic and economic burden of AD among adults and adolescents in KSA.

Materials and methods: A literature search and local expert interviews were conducted to assess the disease burden. Prevalence values were estimated through the literature. International data about health-related quality of life lost owing to AD was adjusted to age and prevalence in KSA. Direct and indirect costs were calculated using a bottom-up approach. Resource utilization data were collected from local dermatologists through online interviews, and indirect costs were based on absenteeism and presenteeism estimates. Validation meetings were conducted with local experts to adjust the final estimates.

Results: The age-standardized health loss per patient due to AD is 0.187 quality-adjusted life-years (QALYs) annually, aggregating to 64 thousand lost QALYs in KSA. The annual average direct cost for a patient with AD was 2924 Saudi Riyal (SAR; 780 USD), totaling 373 million SAR in KSA (99.5 million USD). This value represents 0.2% of the annual health expenditure in KSA. The total productivity loss due to AD was 1.36 billion SAR (363.7 million USD). Overall, the economic burden of AD consumes up to 0.059% of the national gross domestic product.

Limitations: Local quality of life and productivity lost data were not available for KSA, so global averages were used, assuming these numbers also apply to KSA.

Conclusion: Indirect costs represent a large proportion of AD burden in KSA. The disease has a substantial effect on patient quality of life and social well-being. Alleviating the burden might result in significant savings in resources to society.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis is one of the most common skin diseases. Mild cases of the disease cause inflamed and itchy skin, while severe cases may cause painful episodes of itching and cracked skin. Patients with atopic dermatitis and their families suffer lower quality of life as the severity of the disease increases. In countries with hot weather like Saudi Arabia, skin is more susceptible to become dry, so the disease is very prevalent. Therefore, the disease poses a significant quality of life burden as well as an economic burden due to the direct costs of treatment and the indirect costs that arise because patients become non-productive or absent from work or school. Our study aimed to quantify the economic and quality of life burden of atopic dermatitis in Saudi Arabia to understand it's real burden and help decision makers quantify its impact on the patients and society. We conducted a literature search and interviewed local experts to determine estimates of costs and quality of life effects. The results of this study should help in prioritizing treatment disease areas in Saudi Arabia and other countries with similar circumstances.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that can impose a significant burden on patients and their families[1].

Patients with AD may suffer from itching, pruritis, skin redness, and swelling. In more severe cases, the skin might crack or become scaly or lichenified. AD flares are episodes of severe itching and pain experienced by patients. These may worsen at night, resulting in restlessness and inadequate sleep for patients and their caregivers. AD is not a fatal disease, but it has a significant negative effect on patient quality of life because of its effect on daily activities. In the long term, AD predisposes patients to several psychological problems, such as depression for patients who are self-conscious about being itchy and inflamed most of the time[2–4].

Atopic dermatitis occurs as a result of multiple factors, including genetic, environmental, and immunologic. However, the pathophysiology of the disease is not very well understood[5,6]. AD is usually correlated with asthma and allergic rhinitis because these diseases are all related to allergies, genetic defects, and immunologic responses toward allergens[7]. As such, asthma and allergic rhinitis are prevalent among patients with AD[8].

Atopic dermatitis presents as mild to severe disease. The severe form of the disease can be very disrupting and resource consuming[9]. Severity is frequently assessed using questionnaires, completed by patients or their caregivers, usually asking about the frequency and intensity of flares; the area of skin affected; and the presence of redness, papules, scaling, edema or lichenification. Many of these questionnaires exist, but the most commonly used are SCORing Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI), and the Atopic Dermatitis Severity Index (ADSI)[10–12].

Measuring the prevalence and incidence of AD is not an easy task; it is not diagnosed with a laboratory test or a similar objective method[13]. The disease usually develops in childhood. Symptoms may persist throughout one's lifetime or they may improve as patients get older, sometimes resolving completely[14]. AD may develop for the first time in an adult patient, but this is relatively rare[15]. This is why the prevalence of AD is lower in adults compared with children, and most studies related to AD focus on children and adolescents because they represent a larger patient population than adults. AD is more prevalent in countries where the weather is less humid because a lack of humidity can lead to dry skin, which aggravates symptoms of the disease[16,17].

The burden of AD is usually underestimated; beyond the cost of creams and lotions, burden may affect patients in other ways. For example, AD usually flares at night, resulting in inadequate sleep and loss in productivity during the next day. These productivity losses are not limited to the patients but extend to their formal and informal caregivers as well. Furthermore, patients may experience depressive symptoms and a lack of self-confidence because of the disease. These all significantly affect patient quality of life[18–20].

Currently, there is no cure for AD, but several treatment options are available for all severity grades. Treatments usually involve topical emollients and hydrating creams to decrease skin dryness, as well as skin repairing creams. Topical corticosteroids are often used to reduce inflammation and itching, and other creams, such as topical calcineurin inhibitors, are commonly used to control immune response. Systemic immunosuppressants and anti-inflammatories may be used in more severe cases, but efficacy has been questioned[21,22]. New monoclonal antibodies (e.g. dupilumab) and Janus kinase (JAK) inhibitors (e.g. upadacitinib and baricitinib) have been developed as second-line treatments for non-responsive patients. Phototherapy may be used as a treatment option in some cases[22,23].

Previous studies that have assessed the burden of AD globally and in specific geographic areas found that the disease significantly affects the quality of life, productivity, sleep rhythm, mental health, and daily activities of patients[24–26].

In the Middle East, and in the Kingdom of Saudi Arabia (KSA) specifically, there are few publications assessing the burden of AD[27–29], but none has attempted to estimate the humanistic and economic burden in adults and adolescents. A study conducted in 2017 among female patients in Jeddah estimated the prevalence of eczema to be 16.6%[30]. Another recent study estimated the prevalence of AD among Saudi young adults to be 13.1%[27].

This study aims to quantify the humanistic and economic burden of AD among adults and adolescents in KSA. The study results will provide the foundation for evidence-based decision making for policymakers and stakeholders involved in drug selection and budget allocation decisions.

Methods

A literature search and expert interviews were conducted to assess the burden of AD. A bottom-up approach was used to estimate the disease burden. To assess the humanistic burden, the annual quality-adjusted life-years (QALYs) lost due to AD was calculated by multiplying the average utility lost by one patient in KSA by the estimated number of patients. The same approach was used for costs; the average annual cost for treating one patient with AD was multiplied by the estimated number of patients to calculate the total economic burden in KSA. The study included data about adolescents and adults and excluded data about children younger than 10 years based on the World Health Organization's adolescent definition[31]. Ethics approval was not required for this study.

During the study, a conservative approach was used at each step to avoid exaggerated values that might inflate the estimated burden. If reliable and accurate estimates were not available for a data point, the lower values of the available references were used to estimate the burden.

We expressed the humanistic burden in "QALYs lost" rather than other burden of disease measures like disability-adjusted life years (DALYs) and health-adjusted life expectancy (HALE)[32] because the health gain of public health interventions or new medical interventions are standardly reported in QALYs by health technology assessment (HTA)

agencies. So, "QALYs lost" value was estimated to create the potential for calculating the cost-effectiveness of such interventions at the population level. QALYs are among the few methods that allow for comparisons between interventions or across disease areas[33].

Estimating the prevalence

To estimate the humanistic and economic burden, information on the prevalence of AD in patients aged 10 years and older was required. Because quality of life and direct and indirect costs may vary by age and sex, we needed data stratified by those factors. We searched the literature for the required data using two search domains: atopic dermatitis and Saudi Arabia. Synonyms of the disease were also used to find relevant data (e.g. atopic eczema, eczema, prurigo Besnier). Because most prevalence data found in peer-reviewed journals and published studies were limited to a subgroup of patients (e.g. 13- to 14-year-olds), unstratified by age and sex, or restricted to a specific geographic area in KSA[27,30,34,35], data from the Global Burden of Disease study[36] for KSA were used to estimate the prevalence. The Global Burden of Disease study was searched through the Institute for Health Metrics and Evaluation (IHME) database[37] for patients with AD aged 10 years and older in KSA.

Humanistic burden

The annual humanistic burden of AD was defined as the number of QALYs lost for the whole population owing to AD over a 1-year period. To calculate the total QALY loss, the number of patients in each age group was multiplied by the utility lost per patient in the same age group. For example, if the 10- to 14-year-old age group includes 100 patients with AD, and each patient loses 0.1 QALYs on average owing to AD annually, the total humanistic burden for this age group would be as follows: $100 \times 0.1 = 10$ QALYs per year.

To calculate the QALY loss per patient, a literature search was conducted to find studies that provided utility broken down by age group for patients with AD. Quality-of-life values for adolescent subgroups aged 12–14 years and 15–17 years were retrieved from the study by Ezzedine et al.[38], and the quality-of-life values for adult patients aged 18–75 years were reported by Beikert et al. in seven age groups[39]. The values in those studies were used as a starting point to calculate the QALY loss per age group.

Because the age distribution for reporting prevalence and utilities for patients with AD were not identical for all age brackets, the utility for patients aged 12–14 years was used to represent patients 10–14 years old, utility for patients aged 15–17 years was used to represent patients 15–19 years old, and utility for patients aged 18–24 years was used to represent patients 20–24 years old.

Each study measured quality of life using a different questionnaire and on different scales. Hence, conversion of all questionnaire results into one unit was needed, to allow for aggregation of results and comparison. Utility values range from 0 to 1; where 0 represents a person who is dead and 1 represents a person in full health. The EuroQoL 5-dimensions (EQ-5D) index questionnaire is a quality-of-life questionnaire that provides scores in this range; therefore, the quality-of-life scores identified were transformed to EQ-5D index scores.

The study that provided utility scores for the 12- to 14-year age group used the children's version of the Dermatology Life Quality Index questionnaire, and the study providing scores for the 15- to 17-year age group used the adult version. The values were transformed to the EQ-5D index using an online transformation tool[40]. The study that reported adult utility scores used the EQ-5D visual analog scale (VAS) questionnaire. Because the data were presented graphically, the first step was to digitize the values using the WebPlotDigitizer application[41]. Next, EQ-5D VAS scores were transformed to the EQ-5D index. We used the tool developed by Fasseeh et al. to transform EQ-5D VAS values to EQ-5D index values[42]. This tool was based on a linear regression conducted based on five studies that included EQ-5D VAS and EQ-5D index scores for patients with AD in the same subgroup[43–47]. Fifteen data points from these studies were added to the regression model to create the data trend. The regression equation used was:

$$\text{EQ-5D VAS score} = 0.0136 * \text{EQ} - \text{5D index score} - 0.1534$$

We were able to transform all EQ-5D VAS scores to EQ-5D index scores using this equation. Finally, we had all the required age groups utility values reported into a unified score (EQ-5D index score).

Once the utilities for each age group were obtained, utility loss due to AD had to be calculated. To do this, the utility for each subgroup with AD was subtracted from the baseline utility of the average population in this age group. For example, if the baseline utility for an average person aged 10–14 years is 0.95 and the utility of the average AD patient in that same age group is 0.75, then the utility loss due to AD would be as follows: $0.95 - 0.75 = 0.2$

Literature was searched to find studies reporting the baseline utilities for different age groups, either globally or in KSA specifically. The best available reference was a study reporting baseline utility for all age groups in 20 diverse countries[48]. For each age group, the average of the 20 countries was calculated to represent the average utility per age group. This value was used as a proxy for age group utility in KSA. The final calculation for annual humanistic burden was as follows:

$$\begin{aligned}&(\text{number of patients in age group 1}\\&\quad\times\ \text{utility loss per patient in age group 1})\\&\quad+\ (\text{number of patients in age group 2}\\&\quad\times\ \text{utility loss per patient in age group 2})\\&\quad+\ (\text{number of patients in age group 3}\\&\quad\times\ \text{utility loss per patient in age group 3}),\ \text{etc.}\end{aligned}$$

Economic burden

The economic burden of a disease represents the money or resources lost owing to the disease. We adopted a societal

perspective in estimating the economic burden. The economic burden of AD is divided into direct costs, such as the cost of dermatologist visits, pharmaceuticals, hospitalization, and phototherapy sessions, and indirect costs, such as the cost of productivity loss due to the disease. Productivity loss is measured by the number of days that the patient is absent from work or school (absenteeism) and the number of days the patient is at work or school but is not productive (presenteeism)[49].

Direct costs

To calculate the direct costs locally, 2- to 3-h structured expert interviews were conducted with three clinicians who have practical knowledge and real-world experience in treating patients with AD in KSA to ask them about resource utilization (e.g. number of days of hospitalization, type of cream prescribed, frequency of using treatments). The interviews were conducted through online meetings with the experts, who had previously received a questionnaire in preparation for the meeting. Experts were chosen based on convenience sampling.

Interviews were conducted with two dermatologists, and the average values were used to alleviate the effect of individual preferences or bias. One interviewee was from King Khaled University Hospital, which is an affiliated teaching hospital located in the capital of KSA. The other interviewee was from King Abdullah Medical Complex in Jeddah, which is operating under the Ministry of Health. During the interviews, experts were asked to complete the questionnaire, assisted by the research team if clarification was needed. The structured questionnaires used in the experts' interviews were developed through a simple literature search to define the key elements in treating AD. Because the literature revealed that AD is treated differently for patients with mild, moderate, or severe disease, the questionnaire was structured to provide values for each severity grade separately. The resource utilization value was then multiplied by the percentage of patients in a particular severity level (also provided by the experts through the interview), and all severity values were aggregated at the end. The data domains in the questionnaire for the structured interview are shown in Appendix 1 and the questionnaire template is shown in Appendix 2. For example, if 60% of the cases are mild, 30% are moderate, and 10% are severe, and if patients with a mild case use 1 unit per month, with a moderate case use 2 units per month, and with a severe case use 3 units per month, then the calculation for the final average number of units per patient per month will be as follows:

$$(60\% \times 1) + (30\% \times 2) + (10\% \times 3) = 1.5 \text{ units per month}$$

Experts were also asked to provide an estimate for the unit cost of each intervention or treatment. However, this was used only as a guide for validation because the unit costs were abstracted from public prices of products in KSA. Prices were extracted either from the Saudi Food & Drug Authority official website[50], online pharmacy websites[51], online shopping websites (for cosmetic creams) [52], or scientific publications[53]. Data reported for patients in the older age groups were inflated using an online inflation tool for Saudi Riyal[54]. For doses reported as dose per kilogram body weight, the average weight in KSA was used[55].

To calculate the total direct cost per population, the average cost per patient (from the interviews) was multiplied by the prevalence of AD in KSA. The value was adjusted to the percentage of patients diagnosed with AD[56] and did not include undiagnosed patients because patients with AD who have not been diagnosed or treated have no associated direct costs. The final total direct cost equation was:

$$\begin{aligned}\text{Total direct cost} &= \text{average treatment cost per patient} \\ &\times \text{number of patients in the target population} \\ &\times \text{percentage of patients diagnosed}\end{aligned}$$

Indirect costs

To calculate the effect of productivity loss on indirect costs due to AD, absenteeism and presenteeism values were calculated. The first step was to calculate the number of days lost by an average patient due to the disease. We searched the literature for relevant studies, and we identified 17 studies that reported values for the absenteeism or presenteeism of patients or their caregivers due to AD (Appendix 3). Of those studies, 16 included data about absenteeism, 9 included data about presenteeism, 15 included data about the patient burden, and only 2 included data about caregiver burden. The average annual rates of absenteeism and presenteeism for patients were calculated based on all values in the 17 studies. Because this study is a conservative one, caregiver burden was excluded from the calculation owing to scarcity of data and because caregivers were usually associated with children, and our study focused on adults and adolescents. The result of this literature search was the average annual number of days of absenteeism and presenteeism due to AD.

Next, to find the total number of days lost for the whole population due to AD, the number of productivity days lost per patient annually was multiplied by the number of employed patients. To calculate this, the prevalence of the AD population of working age (15–65 years) for male and female patients in each age group was abstracted[37]. Then, we adjusted this value to the unemployment rate in KSA (i.e. percentage of unemployed males and females of working age), and to the labor force participation rate (LFPR; i.e. percentage of employed males and females of working age)[57].

To estimate productivity loss in the AD population in KSA, the number of days lost per patient was multiplied by both the prevalence of male and female patients of working age (adjusted to LFPR and unemployment rate) and the average daily salary. The average salary in KSA was estimated from an internet database[58]. The equation we created to calculate productivity loss is as follows:

$$[\{\text{LFPR male} \times (1 - \text{unemployment rate}) \times \text{prevalence male}\} + \{\text{LFPR female} \times (1 - \text{unemployment rate}) \times \text{prevalence female}\}] \times \text{absenteeism} \times \text{daily salary} + [\{\text{LFPR male} \times (1 - \text{unemployment rate}) \times \text{prevalence male}\} + \{\text{LFPR female} \times (1 - \text{unemployment rate}) \times \text{prevalence female}\}] \times \text{presenteeism} \times \text{daily salary}$$

Total economic burden

The total economic burden was calculated as the sum of direct and indirect costs.

Validation meetings

To validate the research findings, online meetings were held with four local experts in the field to ensure the findings were consistent with local settings and experiences and to make necessary adjustments based on their recommendations. Each validation meeting was managed and coordinated by two research team members (the principal researcher and a senior researcher).

Experts were chosen based on specific criteria: (1) dealing with atopic dermatitis on a daily basis, (2) representing different healthcare systems in Saudi Arabia (Ministry of Health and Population, Ministry of National Guard Health Affairs and University hospitals) and (3) representing different cities in KSA.

During these meetings, all study outcomes (utility values, direct costs, and indirect costs) and their methodology of calculations were discussed in detail with the experts. They discussed the methodology of estimation and recommended better methods or better sources for the data.

Validation meetings were recorded, and transcribed, and corrective actions were taken to adjust the estimates based on recommendations made by the experts. For example, the experts provided a more accurate local reference for the labor force population size and unemployment rate during the validation meeting, and those data were updated accordingly[55].

Results

Based on the Global Burden of Disease database in 2019 (last reported), 343,870 patients with various states of AD severity were present in KSA, representing 1.14% of the total population aged 10 years and older. Prevalence was higher among female versus male patients (1.35% vs 0.99% respectively).

Humanistic burden

On average, a patient with AD accumulates 0.69 QALYs in a life-year with the disease, which is lower than the general population. The age-standardized QALY loss per patient due to AD is 0.187 annually. Based on a total prevalence of about 344 thousand patients in KSA, and after adjusting for subgroups of patients, the total population in KSA loses about 64,000 QALYs annually owing to AD. Table 1 includes the breakdown of humanistic burden in KSA.

Direct costs

Based on the average values provided by two dermatologists *via* questionnaires and subsequent calculations, the estimated annual average direct cost for a patient with AD in KSA is 2,924 SAR annually. For the whole AD population in KSA, the direct costs are estimated at about 373 million SAR. This value represents approximately 0.2% of the annual health expenditure in KSA[59]. Table 2 includes the details of direct costs calculations of AD in KSA.

Indirect costs

Based on the literature search, a patient with AD is absent from work or school for an average of 6.1 days and is present but not productive for an average of 22.9 days annually owing to AD. This translates to an annual loss of up to 285 million SAR and 1079 million SAR due to absenteeism and presenteeism, respectively. The total productivity loss due to AD in KSA per year was estimated at approximately 1.36 billion SAR. This represents 0.05% of the national gross domestic product (GDP)[60]. Table 3 shows the indirect costs calculation details.

Table 1. Humanistic burden of atopic dermatitis in KSA.

Age group, years	Utility among patients with AD, per patient	Baseline utility for general population, per patient	Utility loss for AD, per patient	AD prevalence, no. of patients	QALYs lost annually, per population
10–14	0.76	0.93	0.17	39,970	6,724
15–19	0.70	0.93	0.23	34,702	7,841
20–24	0.77	0.93	0.15	41,643	6,446
25–34	0.73	0.92	0.18	100,224	18,438
35–44	0.71	0.90	0.19	80,067	15,414
45–54	0.68	0.86	0.18	32,629	6,006
55–64	0.54	0.82	0.28	10,496	2,953
65–74	0.71	0.80	0.09	3,154	286
≥75	0.61	0.72	0.11	985	108
Total	–	–	–	343,870	64,215

Abbreviations. AD, atopic dermatitis; KSA, Kingdom of Saudi Arabia; QALY, quality-adjusted life-year.

Table 2. Direct costs of AD in KSA.

Metric	Value	Source
Annual average direct cost per patient	2,924 SAR (780 USD)	Expert questionnaires
Patients with AD aged ≥10 years, *n*	343,870	Global Burden of Diseases[34]
Diagnosed, %	37.10	Hanifin et al.[53]
Total direct cost per population 2019	373 million SAR (99.5 million USD)	Calculation
Annual healthcare expenditure	188 billion SAR (50.0 billion USD)	Global Health Observatory[56]
Percentage of total healthcare expenditure in KSA	0.20	Calculation
Direct cost as a percentage of GDP	0.013	Calculation based on World Bank GDP estimate[57]

Abbreviations. AD, atopic dermatitis; GDP, gross domestic product; KSA, Kingdom of Saudi Arabia; SAR, Saudi Riyal; USD, US dollars.

Table 3. Indirect costs due to AD in KSA.

Metric	Value	Source
Average annual days of absenteeism. n	6.1	Literature search
Average annual days of presenteeism, n	22.9	Literature search
Average monthly salary	6,341 SAR (1,691 USD)	Internet database[55]
Total unemployment rate, * %	7	General Authority of Statistics[54]
Total LFPR, * %	61	General Authority of Statistics[54]
Patients with AD aged 15–65 years, n	299,761	Global Burden of Diseases[34]
Total cost due to absenteeism	285 million SAR (76 million USD)	Calculation
Total cost due to presenteeism	1,079 million SAR (288 million USD)	Calculation
Total indirect cost	1,364 million SAR (364 million USD)	Calculation
Indirect cost as a percentage of the GDP	0.046	Calculation based on World Bank GDP estimate[57]

Abbreviations. AD, atopic dermatitis; GDP, gross domestic product; KSA, Kingdom of Saudi Arabia; LFPR, labor force participation rate; SAR, Saudi Riyal; USD, US dollars.
*Among patients with AD aged ≥15 years.

Total economic burden

Total economic burden (direct and indirect costs) in KSA due to AD is estimated at 1.7 billion SAR annually. Indirect costs are responsible for 79% of this burden.

Discussion

Although AD is a non-fatal disease, it carries a huge burden mainly because of the poor quality of life faced by the patients. AD is ranked 15th in disability-adjusted life-years (DALYs) lost among non-fatal diseases and first in disease burden among all skin diseases[61]. The age-standardized global DALYs burden of AD is comparable to other fatal diseases, such as cirrhosis and measles, and is more than double the burden for scabies and fungal skin diseases[59]. The economic burden of AD in KSA might be more than seven times that of breast cancer, based on a recent retrospective cross-sectional study that estimated the annual cost burden of breast cancer at 13.3 million USD[62] compared with 99.5 million USD for AD as estimated by our study. The methodologies of that study and our study were not exactly the same, but they are comparable in that both studies estimated the annual direct costs of the disease in KSA for adults. The cost per patient is higher for breast cancer, but the high prevalence of AD compared with breast cancer is key in assessing its higher economic burden.

When directing available resources, there may be a lower priority given to treating AD versus fatal diseases because AD mainly affects quality of life rather than years lived. This study provided an estimate of the quantitative burden of AD in Saudi Arabia to guide decision-makers in resource allocation and spending.

Concerning prevalence, the best available age-stratified data were used from the Global Burden of Disease study results; however, the values are most likely an underestimation of the real prevalence according to Saudi experts and validators. Previous studies including AD prevalence in KSA have been conducted and provided higher estimates of prevalence, but these studies were not included here either because they were not stratified by age or sex or because they were confined to a specific geographic region in KSA. The actual prevalence is likely to be higher than reported because a large portion of patients with AD are not diagnosed by a physician. Therefore, estimated values of the burden are most plausibly lower than the actual burden of AD in KSA.

The results show that approximately 64 thousand QALYs are lost annually owing to AD. This may be comparable to other more severe diseases, not only because of the physical pain and suffering that results, but also because of the significant effect that depression, inadequate sleep, and lack of self-confidence have on the quality of life of patients with AD.

The direct cost of a disease is usually what first comes to mind when burden is mentioned. AD is not a disease that usually requires surgeries, diagnostics, or expensive interventions. However, when all factors were aggregated and multiplied by the large number of patients, the burden is considerable. The fact that AD, a disease commonly perceived to be of low morbidity, consumes approximately 0.2% of the health expenditure is alarming. This sizable burden might be attributed to the sheer number of patients with AD and the high cost of medications used by patients with moderate to severe disease. This value is comparable to the contribution of the disease to the national health expenditure in Taiwan (0.314%). However, the value reported in Taiwan

included both children and adults. There are substantial differences between the cost of treating mild versus moderate and severe AD; new targeted therapies can require significant expenditures because the disease is chronic.

Indirect costs are seemingly the critical issue in this disease, contributing to about 79% of the economic burden. Absenteeism and presenteeism can vary between severity levels of AD, but, on average, these are significant enough to generate an economic effect. Since we are adopting a societal perspective, both absenteeism and presenteeism contribute equally to the productivity loss due to AD. We estimated that each year, KSA will lose approximately 1.36 billion SAR as indirect costs owing to AD. This is about five times the direct cost of the disease and accounts for 0.05% of the Saudi GDP, which is one of the highest GDPs in the world[56]. Notably, our study did not address the patient out-of-pocket burden related to multiple skin product trials, which are more difficult to estimate but have been reported to be significant[63,64].

The availability of local data to study disease burden is limited in the Middle East and North Africa region, due to limited accessibility to payers' databases and patient registries[65]. However, the deficiency of high-quality data should not be a barrier to research. Using the available data to conduct research should encourage local stakeholders to improve the quality of data to improve decisions eventually[65].

Limitations

Because there is scarcity of specific data regarding AD in KSA and the neighboring countries, global estimates were used, with an assumption that KSA will follow the same average. This assumption may not always be true because of cultural and climate differences. Efforts were made to adjust values to age, sex, and country, but because some values were not broken-down into these categories, the averages were used instead.

Health-related quality-of-life data were abstracted from studies that were conducted in Germany and France, and the baseline quality-of-life data came from a study that included 20 different countries. Also, we had to use estimates from more than one study because we could not identify all the quality-of-life data for the required age groups from one study. The availability of local quality-of-life data may have improved the accuracy of the results. It is important to note, then, that the quality-of-life values used here are not based on local data but on calculations and estimates.

For prevalence estimates, although the Global Burden of Disease study provided a relatively low estimate (based on Saudi experts' opinions), it was still the best available choice because it included data broken down by age and sex. Since the estimate is probably lower than the actual value, using its values retains our study's conservative nature.

These factors might have caused some inaccuracy in the results. However, because the intention of this study was to estimate the overall country burden of AD, it is assumed that minor inaccuracies would not cause a large deviation and would still provide a very good overview of the comparative burden of the disease. This study should be updated if better local data become available in the future.

The number of experts interviewed was small. However, to make sure the results are valid, we conducted validation meetings with local experts who confirmed the validity of the data and suggested further improvements to increase the data reliability.

Conclusions

Atopic dermatitis poses a significant burden in Saudi Arabia, especially considering the indirect cost. The total economic burden of AD consumes up to 0.059% of the Saudi GDP, which is one of the highest GDPs per country in the world[56]. Also, AD has a significant effect on patient quality of life and social well-being. With optimal disease control, both humanistic and economic burdens may be reduced. Awareness about AD may also prove to be very beneficial in alleviating the huge burden. Our study provides some insight into the burden of this disease in Saudi Arabia, which has not been previously recognized.

Transparency

Declaration of funding

AbbVie funded this research and participated the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. AbbVie sponsored the analysis and interpretation of Data; in reviewing and approval of the final version.

Declaration of interest of financial/other interests

Syreon Middle East was a contractual partner of AbbVie BioPharmaceuticals, Inc. ANF, ShA, and ZK are shareholders in Syreon Middle East. BE and EF are employees at Syreon Middle East. MT, HD, SaA, AR, AJ and TH are employees at AbbVie BioPharmaceuticals, Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ANF, SA, ZK are shareholders in Syreon Middle East. BE and EF are employees at Syreon Middle East. MT, HD, SA, AR, AJ and TH are AbbVie employees and may hold AbbVie stock. For LCA, HA, MAH, AAS, EA, AAT, ME, IH no conflict of interest and no authorship payments were done.

Author contributions

ZK, ShA, BE, ANF, MT were involved in the conception and design of the study. BE and ANF conducted the literature search. EF, BE and ANF conducted the interviews and validation meetings with the experts. MT, HD, SaA, AR, AJ and TH facilitated the interviews and the validation meetings. BE, ANF and ZK conducted the analysis and drafted the manuscript. LCA, HA, MA, AAlS, EA, AA, ME and IH revised the information presented and suggested edits. All authors revised and approved the final version of the manuscript.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Geolocation information

This study was conducted for Saudi Arabia.

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The hidden burden of atopic dermatitis in central and Eastern European countries

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ABSTRACT

Background: Atopic dermatitis (AD) imposes a hidden burden through its negative effects on quality of life and productivity. We aim to estimate this hidden burden in adults and adolescents in Central and Eastern European (CEE) countries.

Methods: We created a burden of disease model to quantify AD's hidden burden. Humanistic burden was calculated by estimating the monetary value of quality-adjusted life years (QALYs) lost, using prevalence data from the Global Burden of Disease study and gross domestic product (GDP) per capita for each country. Indirect economic burden was estimated based on productivity loss from absenteeism and presenteeism, adjusted for labor force participation and unemployment rates. Total hidden burden was determined by combining productivity losses and QALYs lost.

Results: QALY loss due to AD ranged from 1,832 to 58,596 annually in CEE countries, equating to 38 million to approximately 1 billion Euros per country. Productivity losses ranged from 3.6 to 148.9 million Euros annually. The total hidden burden of AD represents 0.11% to 0.43% of the GDP.

Conclusions: Our estimates reflect significant differences in population size, prevalence, and economic strength among CEE countries. Adjusting findings to country-specific GDP provided insights into AD's true hidden burden, offering valuable information for decision-making.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD), commonly known as eczema, is a widespread skin condition causing itchiness and discomfort. While it is well known that treating eczema costs money and affects patients' health, there is more to its impact than meets the eye. Our study closely examined eczema's 'hidden' effects in Central and Eastern European (CEE) countries, such as its impact on work ability and life enjoyment.

We found that eczema's impact is not just about the direct costs of treatment. It also includes how the condition leads to lost workdays and reduced productivity, and more importantly, how it lowers the quality of life for those who have it. This part of eczema's impact, which is not always easy to see or measure, can be just as significant.

Our research is important because it shows that when health officials and policymakers think about how to deal with eczema, they need to consider these hidden effects too. Different countries in Central and Eastern Europe experience these effects in varying degrees. By understanding this, healthcare systems can make better decisions about where to put their healthcare resources. For example, they might decide to invest more in treatments or support that can improve the quality of life for people with eczema.

In summary, our study highlights the need to look at the full picture of eczema's impact. This includes not only the costs of treatment but also how it affects people's lives in ways that are not always immediately obvious.

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Burden of disease; indirect cost; central and eastern Europe; atopic dermatitis; dermatology; quality of life

1. Introduction

In health economics and policy, understanding the full spectrum of a disease's burden, including indirect costs, is crucial for informed decision-making. Detailed insights into a disease's clinical, economic, and humanistic burdens help prioritize research and allocate resources to enhance population health [1,2]. Different studies and databases provide invaluable data on disease prevalence and impact. However, these resources often lack the granularity needed for specific health policy decisions, such as assessing a disease's economic toll through treatment costs or productivity losses in specific regions [3–5].

Currently, many healthcare systems are concerned with health technology assessment (HTA) and resource allocation to overcome the escalating healthcare expenditure [6]. Therefore, the importance of burden of disease studies has grown. These studies help decision-makers better understand the true impact of each disease on society and prioritize which

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disease areas or healthcare interventions are worth the allocation of their limited resources [7].

A disease may affect a patient in numerous ways; it can cause mortality, reduced health-related quality of life (HRQoL), comorbidities, economic burden, and other effects [8]. These effects can be summarized in three components: clinical, humanistic, and economic burdens. While several studies focus on epidemiology to estimate disease burden [4,5], our objectives differ; we use these epidemiological inputs to estimate and monetize the burden.

While some disease burden components, such as epidemiology, mortality, survival, and medical costs, are straightforward and commonly included in such studies, others are harder to quantify. These include humanistic burden, which is based on loss in quality-of-life (QoL), and indirect costs, which reflect productivity losses due to the disease. Nevertheless, these often-overlooked aspects may significantly affect patients and caregivers [9,10].

Atopic dermatitis (AD) is a prevalent, nonfatal chronic skin disease [11]. In Europe, AD affects both children and adults significantly [12], with societal costs of moderate-severe AD in adults estimated at 30 billion EUR [12]. The main burden of AD seems to lie in its hidden costs [13]. A study that focuses only on traditional, easily quantifiable disease burden components would underestimate the true disease impact. Country-specific quantitative data on hidden burdens are essential, enabling decision-makers to have a comprehensive assessment of the real burden.

A burden of disease study in the Middle East and Africa (MEA) aimed to estimate the burden of AD, including hidden costs [14], while another focused on the total burden of moderate-severe disease in Europe [12]. However, Central and Eastern European (CEE) countries lack recent studies of this kind, leaving healthcare decision-makers with insufficient data for evidence-based decisions regarding AD.

This study aims to fill this gap by quantifying the hidden burden of AD for adults and adolescents in CEE countries. Our objective is not merely to present numbers, but to offer a lens through which the real impact of AD can be viewed and understood, providing policymakers with a robust foundation for effective decision-making.

2. Methods

We created a calculation model, based on secondary data from existing literature to estimate the hidden burden components of AD in CEE countries.

We studied 11 countries that are members of the European Union and are geographically located in CEE, namely Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, and Slovenia [15,16].

We used a bottom-up approach to estimate the hidden disease burden components. Since AD can manifest in several severities, we used the QoL and lost productivity values for the general AD population to denote the average severity level among all patients. We multiplied average burden per patient by the disease prevalence to estimate the burden component in each country, as represented by the equation below:

$$\text{Burden component per country} = \text{burden per patient} * \text{AD prevalence in the country}$$

2.1. Estimating the number of adult and adolescent (≥10 years) AD patients in each country

To estimate the number of patients in each country, we extracted prevalence data for each country from the GBD study [17,18], which was provided by age groups. We included all patients starting from the 10–14 years age groups to the 75 + years age group.

Appendix Table S1 shows the prevalence rates and estimated patients' numbers.

2.2. Humanistic burden

The humanistic burden of a disease involves the disease's effect on patients' QoL [9]. HRQoL is usually assessed through self-reported questionnaires completed by patients to assess the disease's impact on various life aspects [19]. Humanistic burden can be expressed in lost quality-adjusted life years (QALYs) reflecting health loss and years of life lost [20]. AD is a non-fatal disease [21], so we only evaluated the effect of health loss for calculating QALYs lost due to the disease.

To quantify AD's effect on QoL, we used HRQoL values reported in the literature. In the context of HTA, HRQoL is often translated into health utility index values, where health utility is defined as a number to describe the health state of a person ranging from death '0' to full health '1' [22]. To estimate the population's disease burden, average health utility values were multiplied by the number of patients in each country. This provided an estimate of the total QALYs lost.

We calculated the health loss per patient by estimating the difference between the utility of a person without the disease and the utility of an AD patient. The difference is due to the disease and is considered loss in HRQoL. Total humanistic burden is calculated by multiplying loss per patient in each age group by the number of patients in this age group.

Average AD patient utility data were abstracted from a recent study that quantified the burden of AD [14]. The utility values for the general population were derived from a study reporting data on Poland, serving as a representative for CEE countries [23]. We used data from Poland as a proxy to all other CEE countries due to the absence of similar studies reporting utility of the general population by age and sex in the selected countries and based on the fact that QoL in these countries are not significantly different [24]. Data in this study was reported in males and females separately; we used the male-to-female ratio from Eurostat reports to adjust the population utility in each country [25]. Then, we recalculated the average utility loss per age group. Utility loss due to AD, and average population data are reported in Supplementary Table S2.

The final calculation model for disease burden was based on the following input data for each age group: general population utility, loss in utility due to AD, and number of patients. The applied formula to estimate the annual total humanistic burden per country was:

$$\Sigma((\text{General population utility for age group x} - \text{Utility of AD population for age group x}) * \text{Number of patient s in age group x})$$

To conduct a fair comparison of different diseases, the unit of assessing the burden was unified, and all burden components were translated into monetary values to be able to compare diseases. To estimate the monetary values of QALYs lost, we adopted a conservative approach of estimating the cost-effectiveness threshold, which reflects the value of one QALY-based on the gross domestic product (GDP) per capita in each country [26]. GDP per capita values were abstracted from the World Bank database [27]. To calculate monetary value of QALYs lost, we used the following formula:

$$\text{Monetary value of QALYs lost} = \text{Annual QALYs lost} * \text{local GDP per capita}$$

2.3. Indirect costs (productivity losses)

To quantify AD's indirect costs, we calculated the number of workdays lost per patient due to AD, then multiplied these values by the patient's average earnings. Patients are considered nonproductive if they are absent from work or school (absenteeism) or present but nonproductive due to lack of concentration or physical abilities (presenteeism), both contributing to reduced productivity, so they were treated similarly concerning indirect costs.

To calculate the indirect costs per population, the calculation was adjusted to labor force participation rate, unemployment rate, and annual working days, to provide a realistic value. These values were obtained from the international labor organization website [28].

For calculating indirect costs, we used an average of 6.1 absenteeism days and 22.9 presenteeism days annually per patient [14]. These values were based on the average for all severity levels. We summed these values to calculate the total number of days where patients are nonproductive due to AD (28.9 days).

The productivity lost was calculated based on the following formula:

$$(\text{Labour force participation rate} * (1 - \text{Unemployment rate}) * \text{Number of patients}) * (\text{Absenteeism} + \text{Presenteeism value}) * \text{Average daily salary}$$

Because these inputs – especially unemployment rate – are usually significantly different between males and females, a separate equation was conducted for each gender, and these were summed to estimate the total value of productivity lost.

2.4. Total hidden burden

To estimate the total hidden burden of AD, we added the monetary value of QALYs lost to the indirect costs. To compare these values and understand which country suffers most from AD hidden costs, we divided the total burden per country by each country's GDP. This provided a value elaborating the percentage of resources lost adjusting to each country's population and economic strength.

2.5. Data adjustment

All data used were for the same year, 2022. This applies to all inputs used in the calculations, including costs, population size, GDP, employment, working days, and salary. Specific prevalence data points were only available for 2019. So we adjusted 2019 data to 2022 by applying the population growth factor for each country during this period, as reported by the World Bank [29]. All data points were converted to a unified time period (one year) to calculate the annual burden. Calculations were performed using Microsoft Excel.

3. Results

3.1. AD number of patients per age group

To estimate AD costs across the entire population, we analyzed prevalence in each country. Table 1 shows the estimated number of patients in each country. Supplementary Figure S1 shows an illustration of the patient numbers among the countries. The total number of adult and adolescent AD patients in CEE countries was estimated at approximately 774,000 patients, and the prevalence of AD among >10 years population ranged from 0.54% to 2.18% for the included countries.

3.2. Humanistic burden

The humanistic burden is represented in this study through loss in HRQoL represented as utility loss per patient. Table 2 shows the QoL loss per age group. QALY loss ranged from

Table 1. Estimated number of patients based on age groups by country (2022 estimate).

Age group	Poland	Hungary	Romania	Czechia	Bulgaria	Slovakia	Croatia	Estonia	Lithuania	Slovenia	Latvia
10-14	43,821	17,400	18,586	13,891	7,764	6,825	5,025	5,219	3,695	2,479	1,807
15-19	27,572	11,553	10,807	7,592	4,746	4,277	3,270	2,711	2,361	1,510	914
20-24	21,192	8,393	6,828	5,109	3,084	3,250	2,591	1,717	1,737	1,088	533
25-34	36,969	12,544	10,558	9,542	5,763	5,629	3,608	3,132	2,607	1,803	986
35-44	37,716	14,505	11,462	10,654	6,060	5,749	3,620	2,760	2,160	1,996	804
45-54	30,846	13,138	12,738	10,118	6,244	4,993	3,784	2,672	2,707	2,039	954
55-64	35,515	12,306	11,914	9,261	6,339	5,203	4,168	2,763	2,963	2,135	1,145
65-74	29,384	11,345	10,778	9,562	6,192	4,172	3,392	2,167	2,090	1,688	912
Above 75	19,350	8,534	7,857	6,441	4,322	2,546	2,809	2,033	2,077	1,488	817
Total AD population	**282,363**	**109,718**	**101,527**	**82,171**	**50,513**	**42,643**	**32,266**	**25,173**	**22,397**	**16,225**	**8,872**

AD: Atopic dermatitis

Table 2. Annual humanistic burden due to AD (QALYs lost per country).

Age range	Poland	Hungary	Romania	Czechia	Bulgaria	Slovakia	Croatia	Estonia	Lithuania	Slovenia	Latvia
10-14	8,404	3,337	3,564	2,664	1,489	1,309	964	1,001	709	475	347
15-19	6,879	2,882	2,696	1,894	1,184	1,067	816	676	589	377	228
20-24	3,779	1,497	1,218	911	550	580	462	306	310	194	95
25-34	7,868	2,670	2,247	2,031	1,226	1,198	768	667	555	384	210
35-44	8,312	3,197	2,526	2,348	1,335	1,267	798	608	476	440	177
45-54	6,345	2,702	2,620	2,081	1,284	1,027	778	550	557	419	196
55-64	11,182	3,875	3,751	2,916	1,996	1,638	1,312	870	933	672	361
65-74	3,415	1,319	1,253	1,111	720	485	394	252	243	196	106
Above 75	2,672	1,179	1,085	890	597	352	388	281	287	205	113
Total QALYS lost (per population)	**58,856**	**22,656**	**20,960**	**16,846**	**10,382**	**8,922**	**6,680**	**5,210**	**4,658**	**3,363**	**1,832**
Weighted Average Utility Loss (per patient)	0.208	0.206	0.206	0.205	0.206	0.209	0.207	0.207	0.208	0.207	0.207

AD: Atopic dermatitis; GDP: Gross Domestic Product; QALYs: Quality Adjusted Life Years

1,832 to 58,856 QALYs annually. On average, an AD patient loses 0.205–0.209 QALYs annually due to the disease. All adult and adolescent patients in CEE lose around 160,000 QALYs annually due to AD.

HRQoL lost values were translated into monetary values through multiplying QALYs lost by the average productivity (GDP/capita) per country. Table 3 shows the estimated monetary values of QALYs lost due to AD. The values reported in the table are not real economic losses, but they represent a proxy for the value of QoL loss due to AD. Values ranged from 38 million EUR to 1.0 billion EUR annually in CEE countries.

3.3. Productivity losses

Indirect AD costs of were represented in productivity losses due to AD. Table 4 shows the indirect costs calculations considering the affected population size, average income per country, labor force participation, and gender-specific prevalence differences. Total indirect costs ranged from 3.6 million EUR to 148.9 million EUR per country annually.

3.4. Total hidden costs

Total hidden costs of AD in CEE countries (including indirect costs and the monetary values of QALYs lost) showed a significant economic loss in each country due to the disease, ranging from approximately 42 million EUR (Latvia) to 1.2 billion EUR (Poland). The total hidden cost of AD in CEE is estimated to be 3.36 billion EUR annually. Table 5 shows the total hidden costs.

Each AD patient had an associated AD hidden burden ranging from 3,013 EUR (Bulgaria) to 6,377 EUR (Slovenia)

Table 3. Monetary value of QALYs lost (2022 euros).

Country	GDP per capita (2022)/EUR [27]	QALYs lost annually due to AD	Monetary value of QALYs lost/EUR
Poland	17,398	58,856	1,023,992,982
Hungary	17,533	22,656	397,238,250
Romania	15,092	20,960	316,320,614
Czechia	26,246	16,846	442,137,697
Bulgaria	13,079	10,382	135,779,348
Slovakia	20,187	8,922	180,108,395
Croatia	17,486	6,680	116,799,725
Estonia	26,905	5,210	140,182,768
Lithuania	23,576	4,658	109,810,527
Slovenia	27,973	3,363	94,072,208
Latvia	20,750	1,832	38,019,556

AD: Atopic dermatitis; GDP: Gross Domestic Product; QALYs: Quality Adjusted Life Years.

Table 4. Indirect cost details due to AD.

Country	Labor force male	15-64 no. of male patients	Labor force female	15-64 no. of female patients	daily salary /EUR	Indirect costs (absenteeism)/EUR	Indirect costs (presenteeism)/EUR	Total indirect cost/EUR
Poland	77%	64,072	65%	125,737	39.1	31,131,114	117,750,982	148,882,096
Hungary	79%	21,873	70%	50,566	30.2	9,601,467	36,316,792	45,918,259
Romania	72%	23,881	54%	40,425	23.9	5,644,941	21,351,545	26,996,486
Czechia	82%	17,622	69%	34,654	50.4	11,661,309	44,107,982	55,769,291
Bulgaria	74%	10,832	67%	21,404	25.5	3,433,068	12,985,310	16,418,378
Slovakia	75%	9,696	68%	19,405	32.9	4,065,516	15,377,494	19,443,010
Croatia	69%	7,002	61%	14,038	34.0	2,752,817	10,412,312	13,165,129
Estonia	78%	5,427	75%	10,327	46.7	3,384,810	12,802,775	16,187,585
Lithuania	74%	3,965	73%	10,570	37.9	2,452,073	9,274,773	11,726,846
Slovenia	76%	3,620	70%	6,951	42.6	1,962,584	7,423,318	9,385,902
Latvia	74%	1,645	69%	3,691	32.7	747,295	2,826,586	3,573,881

AD: Atopic dermatitis.

Table 5. Total hidden costs of AD per country.

Country	Monetary value of QALYs lost/EUR	Indirect costs/EUR	Total hidden costs/EUR
Poland	1,023,992,982	148,882,096	1,172,875,078
Hungary	397,238,250	45,918,259	443,156,509
Romania	316,320,614	26,996,486	343,317,100
Czechia	442,137,697	55,769,291	497,906,987
Bulgaria	135,779,348	16,418,378	152,197,725
Slovakia	180,108,395	19,443,010	199,551,404
Croatia	116,799,725	13,165,129	129,964,853
Estonia	140,182,768	16,187,585	156,370,353
Lithuania	109,810,527	11,726,846	121,537,373
Slovenia	94,072,208	9,385,902	103,458,110
Latvia	38,019,556	3,573,881	41,593,436

QALYs: Quality Adjusted Life Years.

annually. Supplementary Figure S2 shows the details of the hidden cost of AD by patients in each country.

To allow for fair cross-country comparison, we compared the total hidden cost of AD in each country as a percent of its local GDP. Total AD hidden costs as a percent of GDP ranged from 0.11% (Latvia) to 0.43% (Estonia). Figure 1 shows the details of the total AD hidden costs as a percent of national GDP in each country, and Figure 2 shows a map illustration for these values.

4. Discussion

Burden of disease studies helps decision-makers identify key health issues, prioritize healthcare resources, and develop public health strategies. When comparing the burden of common diseases based solely on apparent factors like severity and prevalence, certain conditions with hidden burdens may be overlooked. As a result, they might be less prioritized than more severe diseases that, in reality, are associated with less burden in terms of hidden burden components [30,31].

AD is one of those diseases that imposes a significant hidden burden, [12,14] with indirect costs in some Middle Eastern countries being fourfold times the direct healthcare costs and humanistic burden reaching up to 2.3 times its economic burden [14]. Similarly, in Europe, societal costs of AD were estimated at 30 billion EUR of which 50% were related to productivity losses [12]. That is why it is important to quantify these components of the burden and provide patients with a fair chance of their disease being positioned into its right place among healthcare priorities.

While AD impacts all studied countries, the extent of its burden varies significantly, influenced by various country-specific factors. A primary factor influencing disease burden is the size of the population. As a result, Poland appears to be the most affected by the disease. Nevertheless, the number of AD patients is also high in Poland. Other less populous countries, such as Latvia and Lithuania, also experience the effects of AD relative to their population size.

Based on the GBD study estimates [4], AD prevalence in adults and adolescents in these countries varies significantly (0.54% in Latvia to 2.18% in Estonia). While the absolute difference may appear small, the prevalence in Estonia is actually over four times that of Latvia. This notable disparity, especially among neighboring countries with many commonalities, warrants further investigation to understand the underlying causes of these varying prevalence rates.

Absolute numbers should not be used to compare disease burdens between countries due to varying populations and GDPs. A higher indirect cost does not automatically mean a greater disease burden, as this could reflect larger population size, GDP per capita, services costs, salaries, or other factors. In our study, comparable data across countries

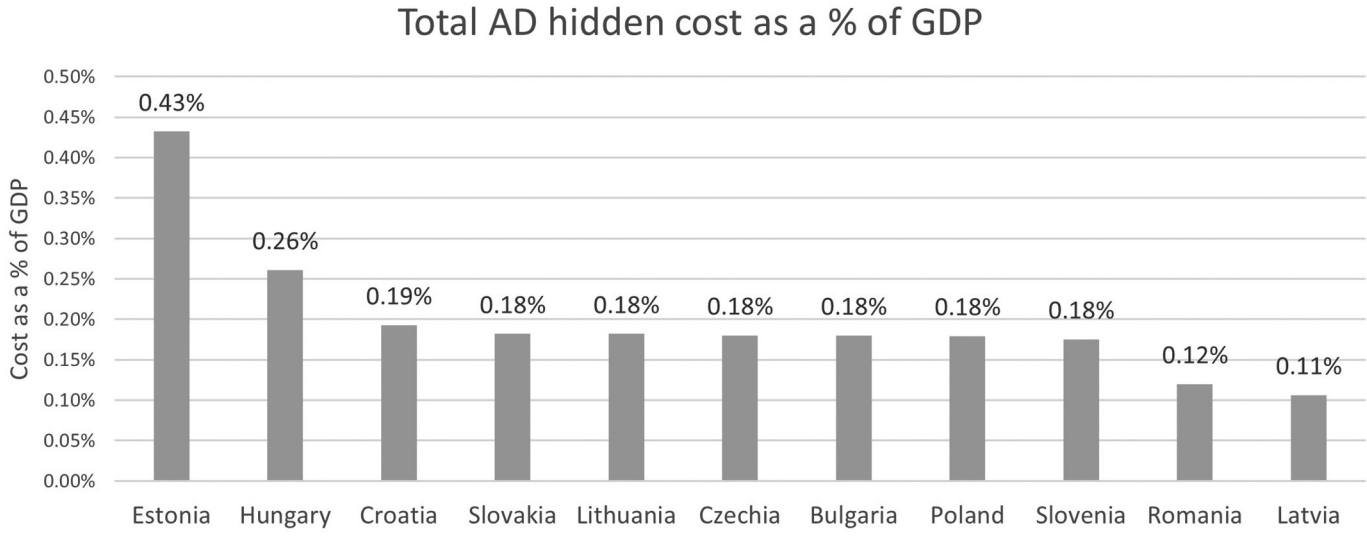

Figure 1. Total AD hidden costs as a percent of national GDP in each country.

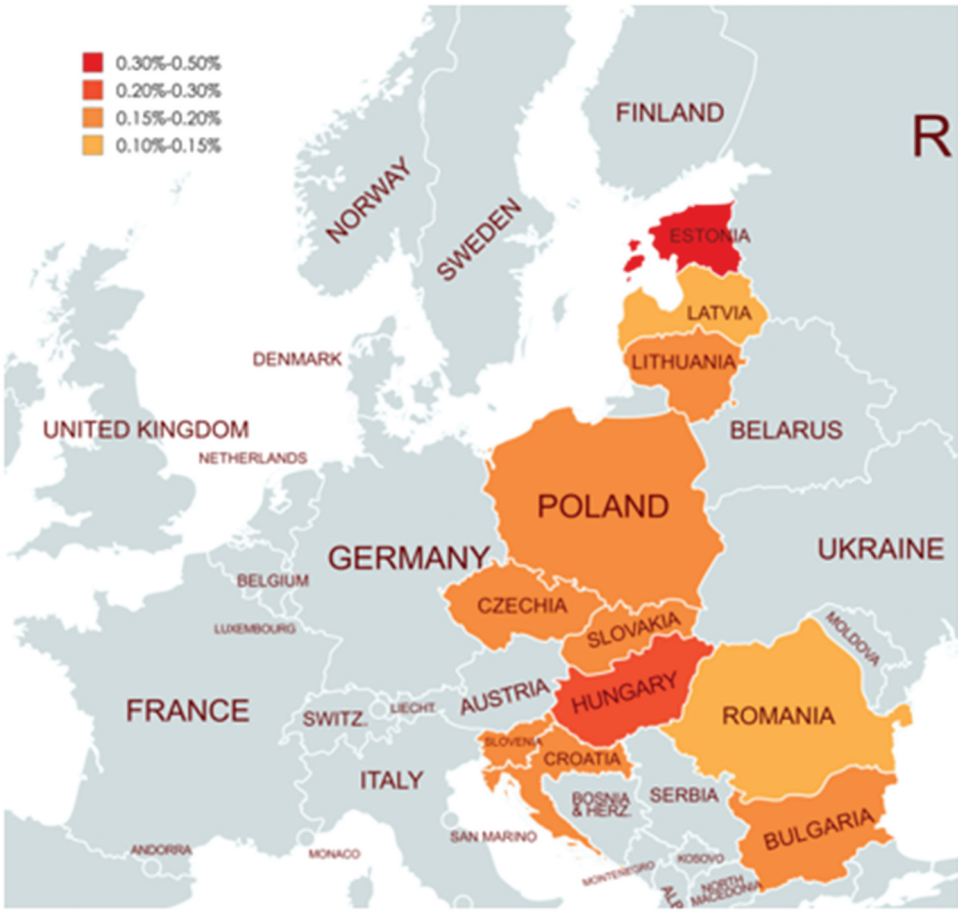

Figure 2. Map showing the total hidden costs as a percent of GDP in CEE countries.

are the total AD hidden cost as a percentage of GDP, since this calculation considers the relative value of the economic burden. This comparison shows Estonia suffers the highest hidden AD burden in CEE, with AD hidden burden consuming around 0.4% of its GDP, versus 0.1% to 0.2% in others. This could be attributed to the high disease prevalence in Estonia (2.18%), compared to less than 1.30% in other countries.

AD significantly impacts HRQoL resulting in an annual 0.205–0.209 utility loss per patient. For the total hidden burden calculation, monetary values of QALYS lost represent the majority of the hidden cost components, with approximately 5 to 13 times the value of productivity losses. This is an important point to consider when allocating resources. Allocating resources to treat or manage AD in CEE countries may have a significant effect on QoL, much more than increasing productivity. While both approaches reduce the total disease burden, decision-makers need to be aware of what to expect from interventions aimed at reducing disease burden.

Previous research has shown a solid relationship between economic burden and AD severity. Despite the absence of curative therapy, effective management of disease progression and maintaining patients in a state of low disease severity can yield substantial economic benefits by mitigating lost productivity and alleviating the overall disease burden. [13]

Another factor that contributes to the complexity of AD's burden is that presenteeism, rather than absenteeism, primarily drives productivity losses [32]. Patients may attend work or school but operate suboptimally, complicating the assessment of the disease's impact and the assessment of interventions' effectiveness. While interventions might not reduce absenteeism, they could enhance productivity, underscoring the importance of precise measurement tools for intervention outcomes.

Our results are consistent with the findings of the study conducted by Augustin et al. for the true costs of AD in Europe [12]. This study estimated the indirect costs at 15.2 billion EUR annually in Europe, while our study estimates this value for selected countries in Europe at an aggregated estimate of about 3.4 billion EUR. This figure is indicative of the CEE region's proportionate share in the overall European context. Notably, Western European countries, possessing higher GDP per capita values [27], consequently have higher absolute values for the disease burden.

The study findings also align with those reported by Shin et al. [33]. This study examined the global and regional trends of allergic disorders, including AD, using data from the Global Burden of Disease study. Both studies highlight the significant humanistic burden of AD, with our study focusing on the burden in CEE, and Shin et al. focusing on the global burden. Concerning the humanistic burden, similar to Shin et al.'s observation that the average Disability Adjusted Life Year (DALYs) of AD remained relatively stable globally, the weighted average utility loss also

in our study shows a minor difference between countries, while the significant differences occur when including the country's populations and GDPs in the calculations.

The estimated hidden cost as a percent of GDP in CEE countries also appears consistent with the study estimating the burden of AD in the MEA region. The cost of AD as a percent of each country's GDP lies within the same range. In the study conducted in the MEA region the range lied from 0.13% to 0.24% [14] after removing the value of healthcare direct costs, while our study presents values from 0.10% to 0.42%. This variation seems logical, considering other differences between the countries in these regions.

By comparing diseases' burdens, decision-makers can make evidence-based decisions on allocating resources toward diseases that create larger burdens on society and healthcare expenditure. Similar studies that quantify the burden are required in other diseases. Such research would further assist decision-makers in efficiently allocating resources among the most beneficial interventions.

The accuracy of our burden of disease estimates is limited, as they rely on population-level data rather than patient-specific details. Population-level data depend on average values and ignore patient- specific values, therefore inaccuracies may appear. However, since the aim of this study is to inform decision-makers for public health-level decision-making, population-level data is considered sufficient. Another limitation to our study, is that we did not consider the caregivers' additional burden in the calculations. This is a conservative approach, as including caregivers' burden would have increased the estimated values of the hidden disease burden. We also acknowledge some other limitations that occurred due to the lack of reliable data, including that disease burden values per patient were not evaluated based on disease severity classification per country. We also used international data for burden element values such as absenteeism and presenteeism values due to the unavailability of country-specific data for AD. We used the general population utility from Poland as a representative for all CEE countries and assumed all other countries' QoL would not vary significantly. Generally, the absence of country-specific accurate epidemiological data hindered the accuracy of our study and obligated us to use international averages with the assumption that the countries will not differ significantly. Finally, the monetization of QALYs approach may not be the most accurate representation of the burden, as converting QALYs into monetary values is not universally accepted. However, it remains a significant metric—as a proxy—to demonstrate its comparative effect among other diseases and other burden components.

5. Conclusions

Although AD is often perceived as a simple, nonfatal disease, our study reveals a considerable hidden humanistic and indirect economic burden in CEE countries. This finding underscores the potential for significant reductions in this burden through allocating adequate resources to manage AD. This disease profoundly impacts both productivity and QoL, leading to substantial economic and social losses. Recognizing and addressing this burden is crucial for improving health outcomes and overall well-being of patients with AD in the CEE region.

Abbreviations

AD	Atopic Dermatitis
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQoL questionnaire
GBD	Global Burden of Disease
GDP	Gross Domestic Product
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
QALY	Quality adjusted life years
QoL	Quality of Life
SF-36	Short Form 36 questionnaire
EUR	Euro
VAS	Visual Analog Scale

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Declaration of interest

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or its supplementary materials].

Author contributions

T Ágh, Z Kaló, A Fasseeh, and B Elezbawy contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Baher Elezbawy. The first draft of the manuscript was written by B Elezbawy. All authors reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Policy Perspective

Strategic Approaches to Reducing the Burden of Atopic Dermatitis in the Middle East and Africa Region

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ABSTRACT

Objectives: Atopic dermatitis (AD) creates a significant burden on patients and society. This study proposes a set of health policy interventions that can reduce the burden of AD in the Middle East and Africa.

Methods: We conducted a scoping review to find relevant actions that have been implemented or recommended to decrease AD burden globally. An expert panel was conducted to discuss the review findings, then experts were surveyed to suggest the most efficient actions. Finally, survey results and recommendations were formulated into key actions to reduce the burden in the Middle East and Africa region.

Results: Recommended actions were related to 5 domains; capacity building, guidelines, research, public awareness, and patient support and education. Several actions related to each domain can help reduce the burden. One of the most advocated recommendations was investing in patient education through trained healthcare professionals. Understanding the disease and learning how to control it is a key cornerstone to treatment optimization and reducing the burden. Multidisciplinary care, publishing defined therapeutic guidelines, and investing in research were the most recommended actions based on the experts' discussion and survey results.

Conclusions: Although the burden of AD is the highest among dermatological diseases, a well-grounded action plan has the potential to reduce the disease burden. Decision makers may develop a national AD action plan by selecting the most relevant items of this study based on their potential impact, feasibility, timeliness, and affordability.

Keywords: atopic dermatitis, dermatology, disease burden, eczema, health policy, recommendations, reducing the burden.

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Introduction

Atopic dermatitis (AD) is one of the most common skin diseases worldwide.[1] Patients with AD may suffer from itching, pruritis, skin redness, and swelling. In more severe cases, the skin might get cracked, scaly, and lichenified. Symptoms are usually worse at night, resulting in restlessness and inadequate sleep for the patients and their families. In the long-term, AD also causes several psychological effects because patients are shy of being itchy and inflamed most of the time, which may cause depression.[2-5]

Although it is a nonfatal disease, AD carries a significant burden, mainly because of the poor quality of life (QoL) faced by the patients and the effect on daily activities. The disease burden of AD is ranked 15th among nonfatal diseases and first among skin diseases.[1] Compared with psoriasis (which ranks second among skin diseases with a high disease burden), AD is associated with nearly double the disability-adjusted life years lost.[1,5] Unlike fatal diseases, resources are not usually allocated toward treating AD because the disease does not mainly affect the life years lived by patients but specifically affects their QoL.[6-9]

The burden of AD is significantly affected by the severity stage.[10,11] Mild disease patients experience less signs and symptoms; therefore, their treatment is usually less costly. Thus, the disease carries a lower psychological and economic burden in patients with mild AD compared with patients with moderate and severe disease. As the condition becomes more severe, it may affect productivity, absenteeism, presenteeism, and QoL and create a higher financial burden on the patients and their families.[12] Managing patients in a less severe stage is key to decreasing the clinical, economic, and humanistic burden of AD, which necessitates patient access to healthcare services and modern therapies.

A study was conducted recently aiming to estimate the economic and humanistic burden of AD in adults and adolescents in 7 countries in the Middle East and Africa (MEA) (Egypt, Lebanon, Saudi Arabia, Kuwait, Algeria, South Africa, and United Arab Emirates [UAE]).[13] The study revealed that the total direct cost in

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the 7 countries was estimated to be more than 460 million USD annually. The direct healthcare cost makes about 0.4% of the total health expenditure in those countries, representing 0.021% of their aggregated GDP (gross domestic product). UAE had the highest annual direct costs reaching around 113 million USD, which accounted for 0.6% of its total healthcare expenditure (0.027% of UAE's GDP). Egypt's annual direct costs were not the highest (about 95 million USD), but the cost as a percentage of healthcare expenditure was the highest, reaching about 0.8% (0.038% of Egypt's GDP). On the other hand, Saudi Arabia and South Africa had the lowest percentage accounting for 0.2% of their healthcare expenditure (0.013% and 0.016% of the GDP, respectively).[14]

The total indirect cost in the 7 countries was more than 930 million USD, whereas the average indirect cost as a percentage of the GDP was estimated to be 0.04%. Saudi Arabia was affected the most with an indirect estimated cost of 364 million USD annually, accounting for 0.046% of its GDP.[15] Lebanon had the least absolute value of indirect costs; however, it accounted for 0.061% of the GDP, the highest among the 7 countries.[13]

The average QALY (quality-adjusted life year) loss per patient for the 7 countries was estimated to be 0.19 QALYs annually. The total utility loss in the 7 countries aggregated was estimated at 334 000 QALYs annually.[13]

The study proved that AD has a significant burden in the MEA. Although the magnitude of economic burden varies between individual countries, AD significantly affects the economy. In general, indirect costs were about 2 times higher than the direct costs, and the total QALYs lost because of AD are comparable to fatal diseases.[13]

Several countries and healthcare systems have conducted changes to their healthcare policy to reduce the burden of AD.[15-17] These policy changes may help to alleviate the symptoms, decrease the number of flares, or reduce the flares' intensity, therefore reducing the clinical, humanistic, and economic burden on the patients and societies.

Continuous integration of new targeted medicines to the routine clinical practice by extending reimbursement coverage is an important step for reducing the disease burden.[18,19] In addition to ensuring patient access to targeted treatments, there are several other policy options to reduce the burden of AD in the MEA.[6] This article aimed to describe a broad range of these policy interventions, which can provide a basis for national AD action plans.

Methods

To create a comprehensive list of strategic approaches to reduce the burden of AD in the MEA region, 5 main steps were implemented: a scoping review to find relevant actions or recommendations, an expert panel to discuss the review findings, an expert survey to collect experts' opinions, a second expert panel to validate the findings, and a final adjustment phase to formulate the results into key recommendations. All of these steps were conducted by 2 teams in collaboration: the research team and the policy experts panel.

The research team conducted the scoping review, created reports for the review to be presented to the experts, created the survey, analyzed the survey results, and formulated the discussion results into draft recommendations. The expert panel included 7 policy experts (1 from each country), in addition to an international health policy expert from outside the MEA region who guided the local experts throughout the process, moderated the discussions, participated in designing the survey, and helped in formulating the draft recommendations into final recommendations. The MEA experts attended the first expert panel, responded to the survey, attended the validation expert panel, provided their votes on the specific actions, and participated in the discussions. They were high-level health policy leaders and decision makers with a holistic view about the healthcare system and the needs and characteristics of their own countries.

Scoping Review

The scoping review was conducted to characterize policy recommendations or actions taken to reduce the burden of AD globally. Interventions that improve patients' access to more effective therapies can provide better disease control and decrease the burden.[7,9,18] Our review focused on these interventions.

The scoping review covered both peer-reviewed studies (Medline via PubMed) and gray literature (Google search engine). Studies were included if they discussed either actions taken by policymakers or recommendations for the decision makers to reduce the economic burden, humanistic burden (effects on QoL), or clinical burden. The search was conducted in September 2021. The search term used can be found in Appendix File 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.100987.

Studies were excluded if the abstract was unavailable or if they did not include any AD specific action or recommendation. There was no restriction on the publication date because the actions can still be effective even if they were conducted long time ago.

For eligible studies, we extracted data about the actions or recommendations for reducing AD burden and the details of implementation. We categorized the extracted actions into 6 domains to help the experts decide the most feasible actions to be implemented.

Expert Panel

An expert panel was conducted with the participation of the 7 policy experts and decision makers and the international policy expert as a moderator. The scoping review findings were presented to the experts, and they discussed each action together with its relevance, applicability, and impact according to their respective countries. After the expert panel, MEA decision makers had the entire problem and solutions crystallized in their minds. Then, they were able to characterize which actions were relevant and applicable to their countries.

Survey

Afterward, an online survey (shown in Appendix File 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.100987) was distributed among the same 7 experts. The first question of the survey was ranking the 6 domains identified from the literature according to their prominence. Next, for the specific actions under each domain, experts were asked to vote whether each action was highly relevant, moderately relevant, or nonrelevant according to their local setting. The survey results were aggregated and analyzed to create a draft list of recommendations that were most advocated by the experts.

Validation Expert Panel and Formulating the Recommendations

After the results of the survey were aggregated by the research team, a second expert panel was conducted with the same experts to discuss these results and formulate specific recommendations and actions to reduce the burden of AD accordingly. The international health policy expert moderated the discussion among

Table 1. Detailed potential policy actions and recommendations from the scoping review.

Domain	Detailed actions
Research related actions	• Quantify the burden of AD on patients and caregivers • Conduct research to assess the loss in QoL due to the disease • Develop a national action plan to reduce AD burden • Study the impact of nurse-led clinics • Study the effect of communication on steroid phobia • Research to identify the gaps in the diagnosis and treatment of AD • Research to enhance patient adherence to medications and special formulations • Conduct research to identify the most impactful communication methods
Capacity building related actions	• Increase the number of dermatologists • Specialized training/education for nurses and GPs in dermatology • Communication skills training for dermatologists • Develop telemedicine to compensate for the low number and uneven distribution of dermatologists among geographical regions • Provide consultation fees to physicians from public resources for patient education
Guidelines related actions	• Using unified and validated measures of AD severity by all stakeholders in the health system • Define specific evidence-based guidelines for treatments • Involve nurses in patient education because they may have more time to spend with patients compared with dermatologists (this would provide better outcomes) • Establish recommendations for multidisciplinary care concept in which the medical team should include dermatologists, pediatricians, allergists, nutritionists, and psychologists. • Develop guidelines for hospitalization of treatment-resistant patients • Monitor and evaluate quality of care with relevant and practical metrics • Encourage shared decision making with patients to improve their adherence (eg, involving patients in the choice of moisturizers) • Prescribe an adequate amount of moisturizers (not more and not less) • Include psychological therapy to the treatment protocol • Individualize patient treatment and care based on specific needs and characteristics of each patient (disease severity, age, educational level, distance from specialist centers, etc) • Update therapeutic plan in scheduled follow-up visits • Monitor and improve patients' adherence
Patient education related actions	1. Content of patient education • Application of topical interventions in an effective way • Allergens that increase the severity and frequency of flares • Benefits and safety of topical corticosteroids to reduce steroid phobia • Avoidance of certain detergents and dealing with laundry • Management of symptoms (eg, itch) 2. Channels of patient education • Involvement of different health care professionals (dermatologists, GPs, and nurses) to patient education • Explanation by healthcare professionals how topical medications should be applied • Printed materials (eg, written plan on disease management) • Other educational channels, such as posters, videos (doctor-patient interviews), widgets, reminders, booklets, and drawings of objects of everyday life 3. General guidelines for education • Educating parents and caregivers in addition to patients • Frequency of follow-up visits with patients • Advice for using online search (what to search and the validity of the information) • Management of the training programs (face to face meetings/online content/how many hours should be invested/group education/educating patients by age groups) • Offering (but not forcing) patient education about management of AD
Patient support related actions	1. Support domains • Provide psychological and emotional support • Provide behavioral support • Improve adherence by detailed communication with patients 2. Patient support channels: • Patient support and patient advocacy groups • Support groups for parents of children with AD • School support programs • Online support programs • Setting up patient organizations and empowering existing patient organizations • Provide financial support to AD patients (disability allowance) to reduce the burden on households

continued on next page

Table 1. Continued

Domain	Detailed actions
Public awareness related actions	• Educate the public about AD to reduce the social stigma and help patients feel more accepted by their peers • Promote smoking cessation to decrease the prevalence of the disease • Encourage the use of powder-free gloves to reduce the incidence • Share a consistent message through different channels across countries and regions

AD indicates atopic dermatitis; GPs, general practitioners; QoL, quality of life.

local experts on which actions were relevant in their countries, and which may be more effective and applicable. The final recommendations were revised by the experts to make sure that there was full consensus about potential policy actions.

Results

Scoping Review

Out of 397 identified studies, 119 were eligible for full-text screening. After screening, only 83 studies that discussed relevant policy actions or recommendations were included for the analysis phase. For these, potential actions were extracted. A list of the actions or recommendations extracted from each study and a list of the included studies are shown in Additional Files 3 and 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.100987, respectively.

The Action Domains

The 6 action domains for reducing burden were capacity building, public awareness, patient education, patient support, guidelines, and research. Each extracted action was categorized to fit into one of these domains. Table 1 shows the details of the potential policy actions and recommendations from the scoping review.

Recategorizing the Domains

During the validation expert panel, experts advised to merge patient support and patient education domains because they are closely related and also to avoid duplication; therefore, the actions were recategorized into 5 domains. Fig. 1 shows an illustration of the 5 final data domains.

For each action domain, several examples of actions were mentioned in the literature. For example, the patient support domain included actions such as "reducing copayments for AD patients" and "conducting patient support groups." Capacity building domain included actions such as "increasing the number of specialists" and "providing communication skills training for nurses and doctors to provide adequate and complete information to the patients." The actions extracted from the literature were categorized into the relevant domains and summarized in the actions map (see Fig. 2).

Expert Panel and Survey

The discussion during the experts panel helped them have a holistic overview about the topic and different approaches to reduce the burden. During the survey, experts were able to clearly define the importance and relevancy of each action from their perspectives.

The survey results showed that for actions related to research, experts considered the following interventions with the highest relevance: developing position articles on AD burden key topics and quantifying the burden and impact of AD on patients and caregivers.

In the capacity building domain, experts considered the following interventions with the highest relevance: having specialized training programs for nurses and general practitioners in dermatology and providing communication skills trainings for dermatologists.

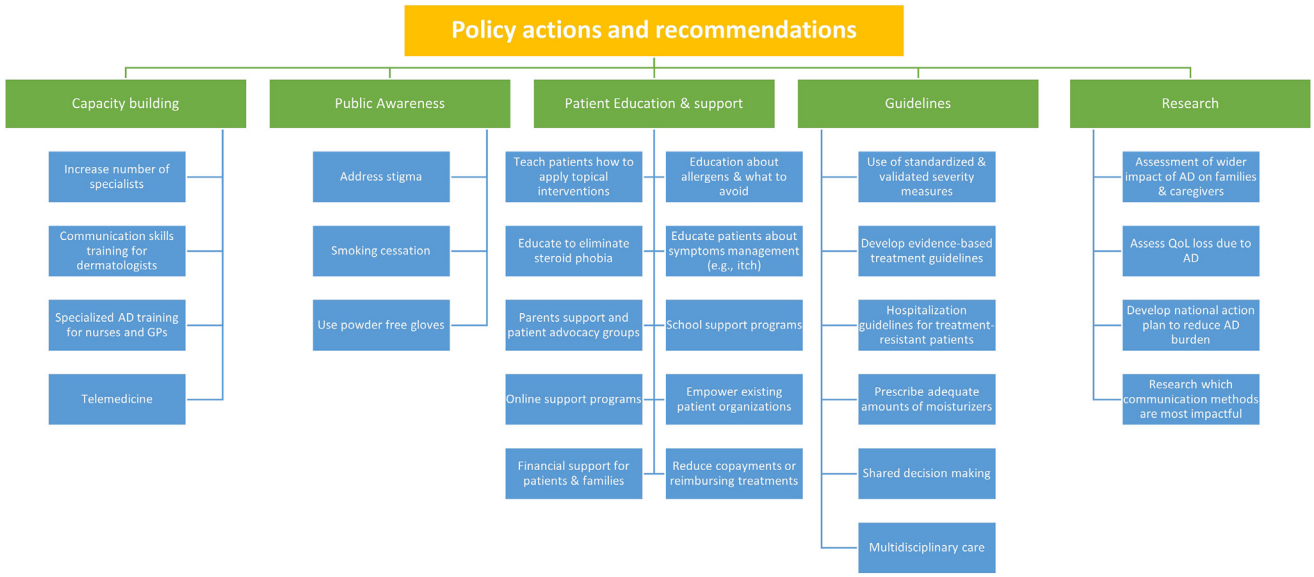
In the guidelines domain, the 2 actions that experts considered most relevant were unifying a measure for AD severity among all stakeholders and defining evidence-based guidelines for treatment.

For patient education and patient support, interventions most advocated by the experts were educating patients how to apply topical interventions and educating them about allergens. Some experts recommended promoting patient advocacy groups. Some also recommended copayments be removed or treatments be reimbursed to enhance patients' access. However, this was a point of debate because this action might be irrelevant in some countries because of different coverage levels; therefore, it was

Figure 1. Domains of the policy recommendations and actions for reducing the burden of AD.

AD indicates atopic dermatitis.

Figure 2. Summary of the potential policy actions and recommendations to reduce AD burden.



AD indicates atopic dermatitis.

formulated to "improving access to necessary care" regardless of the economic status. Another patient support action highly recommended by experts was to prepare specialized supporting materials for adolescent patients who are usually more vulnerable to the negative psychological consequences of the disease such as depression.[5]

For the public awareness domain, experts recommended educating the public about AD to reduce the social stigma and help patients feel more accepted by their peers. Social media can be used to help in increasing awareness.

Beyond the policies and recommendations extracted, experts suggested an additional potential action to reduce AD burden. They suggested involving the community pharmacies and pharmacists in patients' education. This can result in better treatment outcomes and a reduced burden consequently.

Validation Expert Panel

During the validation expert panel, experts discussed the survey results and agreed on the final recommendations. Experts agreed that collaboration among different stakeholders (organizations, pharmaceutical companies, patient advocacy groups, etc) is crucial for reducing the disease burden, especially through developing a country-specific action plan. They emphasized that there will be no one-ranking-fits-all scheme for the domains across all countries; this will depend on the priorities of each country and its available resources.

The survey results showed that capacity building, guidelines, and research domains were considered at a higher priority compared with the other domains. However, after merging patient education and patient support into 1 domain, it was considered the top priority domain. The aggregated results of the voting are shown in Appendix File 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.100987.

Some actions were not relevant for all countries. For example, according to the discussions, steroid phobia is not a problem in Algeria, but it can be an issue in the other countries. Also, in Lebanon and Algeria, there is no need to increase the number of dermatologists, whereas for other countries this may be relevant. This enlightened the experts to agree that this study results

Table 2. Final recommendations and policy action suggested to reduce the burden of AD.

#	Recommendation or policy action
1	Create country-specific action plans for policy interventions that should target different stakeholder groups.
2	Improve patient access to more effective medicines to provide an opportunity to reduce the burden of AD.
3	The relevant group of healthcare professionals (dermatologists, GP, pharmacists, and nurses) should be selected to provide patient education in each country.
4	Empower social media for public awareness about AD and its management.
5	Conduct cost-effectiveness studies with a broader societal perspective (including indirect costs).
6	Prepare counseling materials to help AD patients—especially adolescents—overcome the negative psychological impact of the disease.

AD indicates atopic dermatitis; GPs, general practitioners.

should act as a guidance for decision makers in each country; however, these actions should be fine-tuned for each country's local settings.

Formulating the Results Into Key Recommendations and Specific Actions

Based on the scoping review, analyzing the expert discussion sessions, the results of the survey, and the validation panel, we were able to summarize the key recommendations and specific policy actions that could help decision makers in reducing the burden of AD. These are summarized in Table 2 below.

Discussion

The study results were based on expert recommendations from 7 different countries in the MEA. These countries vary in many aspects relevant to AD, such as economic status, disease burden, affected population, and involved healthcare professionals. Therefore, some actions can be relevant in some countries but not in others. For this reason, the recommendations presented in this article should be adapted carefully in each country to select the most impactful choices according to its needs and resources.

New therapies for AD are more effective[19,20] but also more expensive[21] compared with what was used in the past. Improved patient access to new targeted therapies may significantly improve the outcomes, decrease the severity, and, consequently, decrease the disease burden. However, the cost-effectiveness criterion should be considered before reimbursement decisions, and budget constraints should be managed by appropriate rationing and patient selection in the local clinical guidelines.

According to the experts, a key for reducing the AD burden is treatment optimization. Cornerstones for optimizing the treatment are patient education and capacity building. Patient education can improve patient adherence and improve the efficiency of medication use, while investing in capacity building of healthcare professionals may also contribute to better patient management. Both actions are expected to yield better clinical outcomes and, consequently, reduced disease burden. One hallmark of treatment optimization is managing patients in non-severe stages. Such policy can decrease the disease's clinical, economic, and humanistic burden.

The diversity of the included countries suggests that national action plans should be conducted based on local priorities. The experts highlighted the necessity of streamlining patient pathways, increasing public awareness toward the disease, and collaboration among different stakeholders to decrease the disease burden.

Limitations

The number of experts that participated in the expert panels was low. However, all involved experts were high-level health policy leaders and decision makers; therefore, this low number has limited influence on the validity of proposed recommendations.

Patient representatives were not directly engaged in exploring strategic approaches for reducing the burden of AD. Patient organizations in Middle Eastern and African countries are not established, and policy makers have limited tradition to discuss health policy actions with individual patient representatives. In the future, it is highly important to strengthen the voice of patients in policy recommendations in MEA countries.

Finally, our study does not provide a specific action plan to reduce AD burden instantly; however, it should help each decision maker in his/her country to create their own action plan and start reducing the burden rapidly.

Conclusions

The participating experts in this study were decision makers in their countries. They have been invited to add their insights according to their experience in the local settings and to participate in in summarizing potential strategic action to reduce the burden of AD. Therefore, this article encompasses findings from previous research complemented by feedback from the decision makers. Accordingly, the recommendations presented are based on the consensus of key opinion leaders and policymakers.

This article provides a broad range of policy options to reduce the burden of AD. Decision makers can choose from these actions based on their (1) potential impact by considering local needs and priorities and (2) feasibility by taking into account human resources, healthcare infrastructure, and financial resources. Timeliness and affordability of policy interventions should also be considered in designing country-specific action plans because certain options can take more time and investments before significant reduction of the disease burden can be witnessed.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

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