THE BURDEN OF ATOPIC DERMATITIS IN ADULTS AND ADOLESCENTS

PhD thesis (short version)

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Budapest

2025

1. Introduction

1.1. Atopic dermatitis disease background

Atopic dermatitis (AD) is a chronic skin disease that significantly affects adults and children. AD is often referred to as a pediatric disease, therefore, most published studies focus on the burden on infants and children. However, the disease is also prevalent and significant among adults and adolescents. AD is frequently deprioritized in healthcare due to the perception of being a minor skin condition.

1.2. The burden of AD

AD imposes a considerable burden, largely due to its high prevalence, estimated as 4.0% in children and 2.0% in adults.

Beyond the obvious burden of AD, represented in its direct medical costs, it is essential to evaluate its other hidden burden. This includes less tangible components, such as reduced quality-of-life (QoL) and productivity loss.

Studying the burden of AD is essential to measure the impact of this disease for the individuals and society. This understanding of AD's burden can help mitigating the burden for ultimately better QoL.

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

1.3. Scarcity of studies that quantitatively evaluate all burden of disease components

Since AD is mostly recognized as a childhood disease, published studies predominantly focus on children, while there is scarcity in older patients' studies. Additionally, studies that study the burden in these populations don't provide solutions or actionable interventions to mitigate its burden.

1.4. Aim of the study

We aimed to estimate the burden of AD in adults and adolescents globally and in specific countries, and to provide potential solutions to mitigate this burden. The ultimate goal of the research is to assist decision makers make efficient decisions towards mitigating the burden of AD in adults and adolescents.

Based on these aims, the following research questions (RQ) were formulated: (1) What is the clinical, humanistic and economic burden of AD in adults and adolescents globally?, (2) 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?, (3) What is the monetary value of the hidden burden of AD in in adult and adolescent patients in Central and Eastern European (CEE) countries?, and (4) What actions could be recommended to mitigate the burden of AD?

Findings aim to support decision makers and budget holders responsible for healthcare resource allocation.

2. Methods

2.1. Overview about the studies conducted

We conducted a systematic literature review to summarize the clinical, economic, and humanistic burden of AD in adults and adolescents globally. Next, we provided data for specific countries presenting quantitative values for burden components. These included a study assessing the economic and humanistic burden of AD in adults and adolescents in the MEA, and a study aiming to investigate the hidden burden in

CEE countries. Finally, we presented a study to show potential expert recommendations for mitigating the burden of AD.

2.2. Systematic literature review on the burden of AD

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

We searched PubMed, Scopus, the Cochrane Library, the Centre for Reviews and Dissemination (CRD), and EconPapers for studies including relevant data from 2011 to 2020. In addition, we reviewed grey literature sources including the ISPOR Scientific Presentations Database, as well as the websites of health technology assessment agencies.

Double blinded title and abstract screening was conducted to assess eligibility for full text screening. Full texts screening, data extraction, and risk of bias assessment were conducted by one researcher and revised for accuracy and completeness by another independent researcher. Conflicts were resolved by a senior researcher. Risk of bias assessment was conducted using the Grading of Recommendations Assessment (GRADE) tool.

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

We conducted a study to quantify the economic and humanistic burden of AD in adults and adolescents in major countries in the Middle East and Africa region. This region was selected as it has very diverse healthcare system structures and different levels of economic and social constraints. We included 7 countries to be representative of the whole region. These include Saudi Arabia (KSA), Egypt, United Arab Emirates (UAE), Lebanon, South Africa, Kuwait, and Algeria.

A bottom-up approach was adopted based on the expected patient numbers and the average burden per patient in each country. A literature search, and expert interviews were conducted to estimate the burden.

First, we estimated the number of adult and adolescent AD patients in each country. For humanistic burden, we calculated the loss in QoL due to AD based on multiplying the number of patients per country by the average utility lost per patient. We calculated the the total quality adjusted life years (QALYs) lost by all patients due to AD in each country.

The economic burden included direct and indirect healthcare costs. Direct healthcare costs were represented in direct medical costs. Unit costs for services and drugs were collected from each country. Additionally, resource utilization was assessed through expert interviews in each country to estimate the costs and resources utilization for AD patients. 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. Finally, we calculated the total annual direct cost of AD in each country.

Indirect costs were represented as productivity lost by AD patients due to absenteeism or presenteeism. We adjusted the values to gender, unemployment rate, and the labor force participation rate to accurately estimate the productivity loss.

After estimating all values for humanistic burden, direct medical costs, and indirect costs, the data for each country were validated and readjusted by local experts from the country.

2.4. Hidden burden of AD in CEE countries

The findings of our previous studies revealed that there is a significant hidden burden associated with AD, represented in its deteriorative effects on QoL and productivity losses. Our next study focused on the hidden burden of AD. We aimed to assess the size of this burden in adults and adolescents in CEE countries.

CEE countries were defined as countries that are members of the European Union and are geographically located in CEE. These are 11 countries, including Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, and Slovenia.

First, we estimated patient numbers in each country data from the literature. Then we estimated the humanistic burden through assessing the QoL loss.

To calculate 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 was estimated using the same methodology used in the Middle East and Africa study.

We calculated the total hidden burden as a percentage of its GDP to allow simple comparability among countries.

2.5. Reducing the burden of AD

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

We conducted a global scoping review to identify potential interventions to reduce the burden of AD in September 2021. We included studies that discussed actions or recommendations by policymakers to reduce the burden of AD. We searched PubMed for peer-reviewed studies and Google Search engine for reports or white papers.

Next, an expert panel was convened to discuss the review findings, then a survey was conducted among those experts to collect their opinions on the primary list of potential interventions. Then a validation expert panel was convened to discuss the survey results, identify the most potential actions, and show the pros and cons of each.

Finally, we formulated all findings into five action domains: capacity building, research, guidelines, patient support and education, and public awareness, and created a list of most potential actions.

3. Results

3.1. Systematic literature review on the burden of AD

Out of 3,448 records identified 233 records were eligible for final inclusion in the SLR.

3.1.1. Clinical burden

Itch, depression, and anxiety were the most commonly reported impact parameters, followed by other less frequent outcomes including soreness, skin dryness, and redness. Itch had a very high prevalence ranging from 21% to 100%. The average level of itch was 6 out of 10.

The average depression prevalence among AD patients was 18% as reported by doctors while patients'-reported depression average prevalence was 26%.

For anxiety, prevalence had similarly high values, with an average of 24%. A study reported that 41% of AD patients had moderate or severe anxiety.

3.1.2. Humanistic burden

AD reduces quality of patients' lives through several mechanisms. Psychological impacts were the most mentioned mechanism to reduce patients' QoL. Additionally, other factors like sleep disturbance and limitations in daily activities significantly affected patients' QoL.

QoL questionnaires results were adjusted and aggregated to create a summary of average utility value for each severity, in addition to an average utility value for the unstratified population.

The multivariate regression model showed that male AD patients had a significantly lower QoL versus female AD patients, and that age was not a significant factor for reduced QoL, while higher severities were clearly directly proportional with lower QoL.

3.1.3. Economic burden

Studies that did not subgroup patients by severity showed that AD patients visit dermatologists 8.6 times annually on average, while primary care/ general practitioner visits averaged 16.5 visits annually.

Emergency visits and hospitalizations were not common among AD patients. As severity increased, the frequency of emergency visits and hospitalization increased. Emergency visits frequency was low at an average of 0.8 emergency visits annually, and hospitalizations' average annual frequency was also very low.

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, at 5,246 USD (2020) annually per patient. Total direct costs were 4,411 USD on average, and total indirect costs were 9,068 USD on average.

For indirect costs, on average AD patients lose 68.8 days of productivity annually due to AD, including absenteeism (14.8 days) and presenteeism (54 days).

3.2. Humanistic and economic burden of AD in the -MEA region

3.2.1. Humanistic burden

Due to the absent or negligible effect of AD on survival, annual utility loss was assumed to be equal to annual QALY losses. Average utility losses due to AD range from 0.09 to 0.28 per patient.

Country-level QALY losses differed significantly between countries ranging from 7,840 QALYs annually in Kuwait, to 102,238 QALYs in Egypt, especially due to different population sizes.

The weighted average utility loss per patient ranged 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.

3.2.2. Economic burden

3.2.2.1. Direct healthcare costs

Annual treatment costs for an AD patient vary widely among 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 Arab Emirates. However, direct comparisons of annual treatment costs across countries should not be directly compared, as the number of patients differ significantly between countries, influencing the overall expenditure.

3.2.2.2. Indirect costs (productivity losses)

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. Country-specific productivity losses showed a wide range of economic losses due to absenteeism and presenteeism. Indirect costs as a percentage of GDP ranged from 0.022% in Algeria to 0.061%in Saudi Arabia.

3.2.3. Total burden

The total burden includes direct costs, indirect costs, and monetary value of QALYs lost. 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.

AD consumed values ranging from 0.164% of the national GDP (Egypt), up to 0.265% of the national GDP (Kuwait), which is considered a significant proportion for a non-fatal skin disease.

3.3. Hidden burden of AD in CEE countries

3.3.1. Humanistic burden

Total QALYs lost in each country ranged from 1,832 QALYs in Latvia to 58,856 QALYs in Poland. The weighted average utility loss ranged from 0.205-0.209. The estimated monetary values of QALYs lost due to AD ranges from 38 million € annually in Latvia, to more than 1 billion € in Poland.

3.3.2. Indirect costs (productivity losses)

Presenteeism represent the larger proportion of indirect costs due to AD. Estimated total indirect costs ranged from 3.6 million EUR in Latvia, up to 149 million EUR in Poland.

3.3.3. Total hidden burden

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

We compared total AD hidden burden values as a percentage of the national GDP of each country. This showed 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.

3.4. Reducing the burden of AD

3.4.1. Scoping review

We identified 397 hits from the scoping review , of which 83 were eligible for inclusion. The actions extracted were categorized into 5 action domains: capacity building, public awareness, patient education and support, guidelines, and research.

3.4.2. Expert panels and survey

The experts’ panels and survey helped to formulate the action domains into specific actions, and to prioritize those actions with a higher impact.

Capacity-building actions prioritize increasing the number of specialists and providing specialized training for healthcare professionals, including dermatologists, nurses, and general practitioners. Public awareness domain initiatives focus on addressing social stigma, promoting smoking cessation, and encouraging the use of preventive measures like powder-free gloves. Patient education and support domain emphasizes teaching patients the proper use of topical treatments, educating about allergens and symptom management, and overcoming steroid phobia. Supporting patients extends to empowering advocacy groups, providing financial support, and creating school programs to improve the daily lives of patients and their families. Developing evidence-based 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.

3.4.3. Final recommendations

The list below includes the final shortlist recommendations and policy actions suggested to reduce the burden of AD

- Create country-specific action plans for policy interventions targeting 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.

4. Discussion

4.1. Overview of the research outcomes

Although AD is often considered non-serious due to its non-fatal nature, our research shows it imposes a significant burden on adult and adolescent patients, particularly in severe cases. While direct medical costs are well documented, the hidden societal burden incurs considerable indirect economic costs. Given its the high global prevalence, AD's overall burden sometimes exceeds, that of more severe conditions; for instance, GBD's age standardized DALY rate for AD surpasses liver cirrhosis due to its widespread population impact.

4.2. The clinical, humanistic and economic burden of AD in adults and adolescents globally

Our SLR highlighted AD's clinical burden (comorbidities, signs and symptoms) and factors reducing QoL, findings concordant with published research showing itch, anxiety, depression, sleep disorders and productivity losses. However, burden components vary by country, so we conducted regional studies to quantify the burden in each country.

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

Our MEA study valued QoL reductions and found AD consumed 0.164–0.265% of GDP across included countries, highest in Kuwait (0.265%) and lowest in Egypt (0.164%).

Except in Egypt, indirect costs exceeded healthcare costs—reaching over three times in Saudi Arabia; in Egypt, direct costs dominated (63%) due to relatively lower salaries. Saudi Arabia's burden total was 0.249%, and UAE was 0.247% highlighting absenteeism and presenteeism losses. Algeria's direct healthcare burden was 0.046%, rising to 0.209% including QALYs (0.163%). Lebanon had the highest indirect cost burden (0.061%), for a total of 0.207%, underscoring productivity loss as a key target.

4.4. Hidden burden of AD in CEE countries

Poland had the highest absolute hidden burden (>€1.1 billion annually), with other countries ranging from €42–443 million. In all countries, QALYs comprised 87–92% of hidden costs. Adjusted for GDP, Estonia led at 0.43% (prevalence 2.18%), followed by Hungary (0.26%), with Romania 0.12% and Latvia 0.11%, reflecting prevalence, management strategies or data methods. These findings align with prior estimates of indirect AD costs in Europe (€15.2 billion) and proportionally reflect CEE's share (~€3.4 billion), consistent with global literature on AD's humanistic impact.

4.5. Actions to reduce the burden of AD

Our final study delivers comprehensive solutions for decision-makers, proposing specific actions across five domains to reduce AD's burden. Decision-makers should assess the relative burden in their settings to select suitable actions. Experts stressed that policies effective in one country may not succeed in another, underscoring the need for tailored, country-specific action plans.

Our last study was conducted to complement these studies by delivering comprehensive solutions for decisionmakers. The proposed actions to reduce the burden of AD concludes our research. Decisionmakers are expected to assess the relative burden of AD within their specific settings and select the suitable potential actions, to reduce the burden of AD and improve health outcomes.

Experts advised that 5 domains of actions are potential for mitigating the burden of AD. Our research provides 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. This emphasizes that actions should be assessed and adjusted to country-specific settings. Therefore, experts agreed that effective reduction in the burden of AD will require country-specific action plans.

5. Conclusions

AD is a prevalent skin disease associated with several levels of severity. Without quantification, the disease seems to be a simple, non-fatal dermatological condition with a low burden among other disease areas. Experts are usually not concerned with allocating resources to mitigate such a simple disease.

Our research findings reveal the significant burden of AD, which is comparable to more severe diseases. This high burden stems from its high prevalence, and the hidden burden through effects on reducing productivity and QoL. Results reveal that around 20% of an average patient's QoL is lost due to AD.

Economic burden of the disease is significant. But also, AD's indirect costs have a burden higher than the direct costs. Hidden burden components are the major contributors to the disease burden, further emphasizing that the disease burden is usually underestimated.

Simple actions such as educating patients and improving public awareness can significantly reduce the burden.

Decisionmakers are recommended to use the findings of this study to assess the burden in their countries and tailor specific action plans to reduce the burden of AD effectively.

6. Bibliography of the candidate's publications related to the thesis

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