

Indirect costs of atopic dermatitis (AD) – systematic review and Polish perspective

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Abstract

OBJECTIVE: Atopic dermatitis (AD) is a common chronic, pruritic inflammatory skin disease. It is associated with a high personal burden of illness and economic consequences. The main purpose of this analysis is to present the indirect costs of atopic dermatitis, including their specific aspects.

METHODS: The analysis was based on a systematic review of the literature (23 October 2019). Keywords related to indirect costs and AD were used in the search strategy.

RESULTS: 35 publications were included in the final analysis. They showed that a significant reduction in the quality of life of patients with atopic dermatitis is associated with high costs from a social perspective. A systematic review of the literature indicates that the costs arising from the absence of AD patients at work (absenteeism) or their reduced effectiveness during the performance of work duties (presenteeism) are much higher than those of people without AD (weekly productivity loss between 3-5%). Factors particularly affecting the amount of costs (direct and indirect) generated by AD include the severity of the disease and its control, as well as the type of treatment used and the patient's response to it. In Europe and USA, annual indirect costs (only productivity loss) due to AD are estimated at 2,3 billion EUR and 619 million USD respectively. Indirect costs in patients with atopic dermatitis are significantly higher than in people without this condition, which is due to reduced work productivity. Available literature indicate that the more advanced the form of AD, the greater the loss of productivity, and thus the higher indirect costs, and this observation is confirmed by data from various countries. The amount of indirect costs in AD is higher in the case of an uncontrolled form of the disease than in the case of a controlled disease. The use of ineffective treatment significantly in-

creases the indirect costs of atopic dermatitis. Currently therapeutic options available in Poland are not sufficiently effective to provide disease control in all patients with AD, are characterized with adverse reactions, their use is limited in time and therefore their use will not bring savings in indirect costs in patients with severe AD.

CONCLUSIONS: In this systematic review, we observed some aspect that likely have a major impact on the indirect costs in patients with AD: effectiveness of treatment, disease control (maintenance therapy between successive exacerbations). Ineffective treatments significantly increase the indirect costs of atopic dermatitis.

Objective

The occurrence of disease states may result in a decrease in the level of human activity, both social and economic. A healthy citizen is a wealth for the state and society, enabling socio-economic development, production of material goods, and thus a sufficiently high level of quality of life. From an economic point of view, decreasing the level of activity means a loss for the economy and for society. For this reason, especially in recent years, in the context of demographic, social and economic changes, health began to be seen not only as a condition for the development of the individual, but also of the entire civilization.^[5]

Costs in the analysis of health technology assessment are understood as the value of all burdens resulting from the course of the disease and its treatment. By default, in this area, costs that can be measured in monetary units are divided into direct - expenditure related to the disease and treatment and indirect - resources lost due to the disease and its consequences. There are also unmeasurable costs - so-called non-measurable costs.^[5, 6]

Usually, the analysis of cost of illness includes direct costs, i.e. expenses incurred for health services (including medicines) and indirect costs, which mainly include expenses in the field of social security, such as costs of disability pensions, social pensions, rehabilitation benefits and benefits sick leave and costs of incapacity to work due to illness borne by employers. However, only the summary of all cost data and their analysis show the complexity and scale of the problem. They make us aware of the need to treat the disease, especially chronic disease, as an economic issue.

Indirect costs are typically expressed in terms of the costs incurred from mortality and absenteeism and the reduced productivity while an affected employee is still working (Table 1).^[7]

| Component | Costs |
|----------------------|---|
| Mortality | Employee replacement Effect on family and friends Value of lost future income |
| Morbidity | Lost wages • Paid sick-leave days • Unpaid sick-leave days • Payroll and benefit costs for absent employee Loss of vacation and personal leave Disability Lost leisure time Idle employer assets |
| Reduced productivity | Return-to-work productivity Employee's health capital investment On-the-job training New-hiring administration and training Motivation and uptake of training Teamwork and communication Institutional effect among coworkers Effect on family members |

Table 1. Components of Indirect Costs ^[7]

The basic division, which is introduced as part of the categorization of costs of lost productivity, refers to the person or persons whose productivity is assessed - the patient or their caregivers. The productivity of each of these groups of people can be assessed in relation to paid (paid) work, unpaid work or free time. In relation to paid work, there is a loss of productivity resulting from the employee's absence from work (absenteeism) or costs resulting from reduced effectiveness of work (presentism), when - despite illness - he undertakes to perform his professional duties. There are also costs associated with the loss of productivity of care-givers (informal care), as well as the loss of productivity in relation to unpaid work and lost free time.^[5]

Description of atopic dermatitis

Atopic dermatitis (AD) is one of the most common chronic dermatological diseases, occurring both among children and adults, caused by both genetic factors and hypersensitivity to environmental factors. Moderate-to-severe AD is associated with significant reduction of quality of life and self-esteem, and negatively affects patient's mental health and professional life. Treatment of atopic dermatitis is often bothersome and long-lasting.

Atopic dermatitis consequences:

- Insomnia
- Lack of concentration at work
- Social stigmatization
- Changes of outfit and activity
- Impact of finances
- Depression /anxiety disorder.

Estimated on the basis of epidemiological data, the percentage of patients in Poland is in the range of 4,3% - 5,3% in children and 2,24% in adults.^[2] This means that in Po-

land, over 335,000 children are affected by atopic dermatitis and 705,000 adults. 22,63% of adult's patients with atopic dermatitis, has moderate or severe disease (159,000 patients) and 6,58 has severe disease (46,000 patients).^[2] According to European data, this is the fourth most common skin disease occurring in adults after warts, acne and contact eczema.

Atopic dermatitis is a commonly underestimated disease because it does not directly threaten life. Despite this, it is a serious social problem, because it is a common disease, chronic, lowering the patient's quality of life, it can cause serious complications such as erythroderma, cataracts, suicidal thoughts and attempts. AD is affecting increased absenteeism at work and causing psychosocial problems in both children and adults. The characteristic symptoms of AD are mainly itching. The severity of itching is greatest in the evenings and during the night, which reduces the amount of sleep and translates into fatigue during the day.^[8] Polish data indicate that itching occurs in all patients, while in 70% of patients it is severe or very strong (patients' feelings).^[9] As the disease progresses, papillary-exudative lesions, bleeding, erosions, vesicles, and scabs occur in the course of inflammation.^[10, 11, 12] The severity of AD is assessed according to the SCORAD scale into three forms: mild, moderate and severe. Approximately 45% of patients have mild AD, 45% are moderate and 10% severe. The most common symptoms in mild to moderate AD are redness, itching and dry skin, and the lesion area is relatively limited. Patients with a severe form of the disease are more likely to have papulo-effusive lesions, bleeding, and vesicles and erosions, and symptoms such as pruritus, peeling, and skin cracking are so bothersome that they make it difficult for patients to function daily and perform everyday activities.^[3] Patients with severe AD have an average of 16 exacerbations of disease symptoms per year, while patients with mild AD have 3 exacerbations per year.^[13]

All these elements affect the quality of life of patients with AD. Sleep related disorders are reported by 65% of patients with AD.^[9] This clinical aspect is intensified in patients with severe disease, where sleep disturbances occur up to 162 nights a year.^[15] Sleep disturbances translate into a deterioration in the well-being of patients with AD, fatigue during the day and problems with concentration, and consequently a decrease in efficiency at work and during daily activities.^[8] The disease also contributes to the lowering of patients' self-esteem due to the condition of their skin (80% of patients) and influences decisions related to the way of dressing (90% of patients).^[9]

Symptoms of severe AD can translate into problems with concentration and psyche, which can lead to the development of depression and anxiety.^[9] Depression due to atopic dermatitis is reported by 27% of Polish patients,

while as many as 14% are accompanied by suicidal ideation. According to WHO estimates, the incidence of suicidal ideation in the general population is estimated at 2%. In the population of Polish psychiatric patients, the percentage of patients with suicidal ideation is 20%, including 12% in patients with anxiety and neurotic disorders and 35% among patients with affective disorders such as depression.

In addition, AD is often associated with other allergic and atopic diseases, and its complications include frequent and recurrent skin infections, food intolerance and eye diseases, including cataracts, conjunctivitis and keratitis.^[11, 14]

All the above-mentioned aspects related to the course of AD are affecting the need to spend direct medical costs as well as causing indirect costs (Figure 1). The direct costs of AD include mainly visits to specialists (dermatologist, allergist), expenses for symptomatic and causal treatment (ointments and creams containing glucocorticosteroids, immunosuppressive drugs) and expenses for other products used in treatment, including agents for atopic skin care (emollients) or wet dressings. Indirect costs will consist of absenteeism (absence from work due to the need to visit a doctor or take a longer sick leave due to the severity of the symptoms) and presentism (reduced productivity during the performance of official duties due to the presence of sickness symptoms). The costs of presentism and absenteeism together are the costs of lost productivity.

The main purpose of this analysis is to present the indirect costs of atopic dermatitis, including their specific aspects.

COSTS OF ATOPIC DERMATITIS (AD)

Direct costs

- Visits to dermatologists and allergists
- Transport for ambulatory visits and to the pharmacy
- Expenses for prescription drugs, ranging from locals steroids and ending with biological medicines
- Expenses for over-the-counter medications and products such as emollients
- Procedures such as wet dressings and phototherapy
- Hospitalization or emergency care
- Skin cancer screening in patients treated with psoralen or phototherapy

Indirect costs

- Absenteeism resulting from the need to take time off, e.g. for medical visits or inability to perform official duties
- Presentism resulting from a lack of concentration due to persistent itching
- Loss of employment due to illness
- Social burden, including shame or social interaction that prevents work
- Psychological burden caused by insomnia due to itching, depression, anxiety or suicidal thoughts due to illness

Figure 1. Direct and indirect costs in AD

Methods

This analysis has been prepared based on a systematic review of the literature. A systematic search in medical information databases (MEDLINE, Embase, ISPOR, Scopus, Web of Science, Google Scholar) was conducted on October 23, 2019. Details of the inclusion criteria and search strategies are presented in Supplementary materials.

Results

As a result of the search, a total of 3,449 bibliographic items were found. Additionally, one non-publish analysis was provided by co-authors.^[33]

After the initial selection of titles and abstracts, 83 papers were qualified for further analysis, while a total of 35 publications met the eligibility criteria, from which information was taken for the analysis (Figure 2). The analysis included publications that presented data on indirect costs (absenteeism, presentism, loss of productivity) in patients with atopic dermatitis.

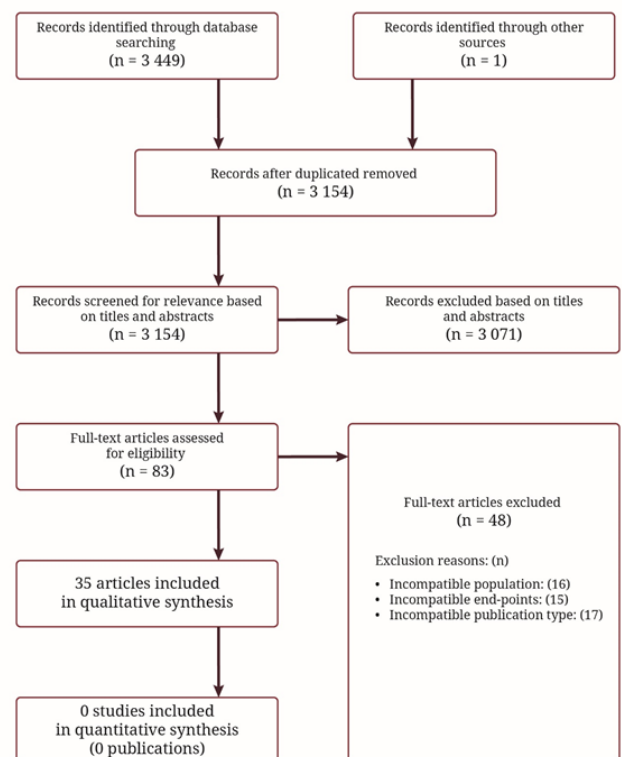


Figure 2. PRISMA flow diagram

In AD, the main direct costs include expenses for visits to specialists such as a dermatologist or allergist, as well as expenses for treatment, including prescription products - from ointments and creams containing glucocorticosteroids to systemic drugs.^[10] Additional direct costs will also be expenses for other products used in treatment, including funds for atopic skin care (emollients) or wet dressings. In turn, the main indirect costs will include the costs of absenteeism - absenteeism due to the need to visit a doctor or take a longer sick leave due to the severity of the symptoms - and presenteeism - reduced productivity during the performance of official duties due to the presence of sickness symptoms. The costs of presenteeism and absenteeism together are the costs of lost productivity.

A significant reduction in the quality of life of patients with atopic dermatitis is associated with high costs from a social perspective. A systematic review of the literature indicates that the costs arising from the absence of AD patients at work (absenteeism) or their reduced effectiveness during the performance of work duties (presenteeism) are much higher than those of people without AD (weekly productivity loss between 3-5%). Factors particularly affecting the amount of costs generated by AD include the severity of the disease and its control, as well as the type of treatment used and the patient's response to it.^[1]

We summarize our findings from the literature review, with a focus on presenting published estimates of indirect cost of AD in Europe, USA and Poland, followed by a comparison of indirect costs between AD and the general population; a description of factors affecting indirect costs in AD (disease severity, disease control, type of treatment used).

Indirect costs in AD

Annual loss of productivity costs of atopic dermatitis for all ill patients with AD in Europe are estimated at 2,3 billion EUR (370 EUR per 1 patient).^[15] Using the same calculation methodology and assumptions for Poland, indirect costs related to AD can reach 199 million EUR. In USA loss of productivity costs of AD in 2004 were estimated at 619 million USD (in 2004 USD).^[45]

Polish ZUS (Polish Social Security) data for 2018 shows, the costs associated with atopic dermatitis due to sickness absence and disability benefits amounted to almost 7,3 million EUR (68.9 thousand absence days and 74 disability benefits).^[16] Compared to other skin diseases, the number of days and costs of AD absenteeism exceeded the number of days of absenteeism due to lupus erythematosus and skin cancers other than melanoma.^[16]

In the UK, indirect costs caused by absenteeism due to atopic dermatitis (7,38 GBP per capita) were higher than

other common conditions such as benign prostatic hyperplasia (1,04 – 1,53 GBP) or venous ulceration (6,73 GBP).^[23]

In the USA, the total number of days absent from work due to AD was estimated at 5.9 million (yearly).^[27]

Loss of productivity of AD patients relative to the general population

Indirect costs in patients with atopic dermatitis are significantly higher than in people without this condition, which is due to reduced work productivity.^[14] In USA, weekly loss of productivity of patients with AD is significantly greater than that of people without AD by approximately 7.5 percentage points.^[17] In Europe, this difference was also statistically significant and amounted to around 3 percentage points, mainly because of presenteeism.^[19, 20] The higher indirect costs in patients with atopic dermatitis relative to the general population is caused by a greater frequency of patients being on sick leave and reduced effectiveness at work, due to physical ailments hindering concentration. Data from Finland shows that 70% of patients with atopic dermatitis were on sick leave at least once a year for whatever reason, and 20% of all reasons for absence from work were atopic dermatitis.^[21] In Denmark and Netherlands absence from work due to atopic dermatitis was estimated at 11,6 and 5,7 days per year (an average per patient), respectively.^[24, 25] In the newest study from Europe 57% of AD patients were absent at least 1 day, 31% were absent 1-5 days and 25% were absent more than 6 days in a year.^[26] 32% of patients with atopic dermatitis experience a decrease in income due to illness, which may be due to the need for them to incur additional medical expenses. As many as 38% of patients with atopic dermatitis declare that the disease had an impact on the choice of their career path, and 40% admit that they have been out of work at least once in their life, i.e. much more often than people without AD (29%).^[21, 22, 24]

Factors affecting indirect costs in AD Disease severity

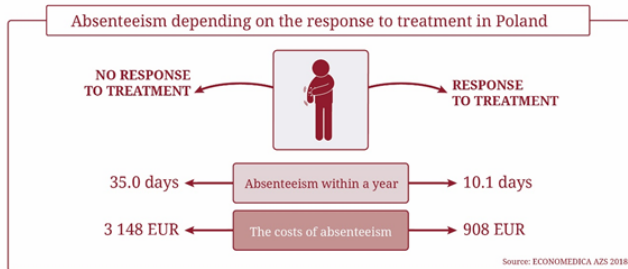
Available literature indicate that the more advanced the form of AD, the greater the loss of productivity, and thus the higher indirect costs, and this observation is confirmed by data from various countries. Based on data from USA, loss of productivity in patients with AD is strongly correlated with the severity of the disease - it is twice as high in patients with severe disease compared to moderate.^[28, 29] In one study, absenteeism reported in patients with moderate AD was 1.7%, compared with 3.3% in patients with severe AD,^[28] while presenteeism 11.5% and 23.9% respectively and total productivity loss 12.2% and 23.9% respectively. In second study total productivity loss in patients with severe AD were 47.4% while 23.7% with moderate AD.^[29] In European study conducted in 8

countries, statistically significantly higher number of days of absence from work in a year due to AD was reported in the group of patients with severe (5.3 days) than moderate (1.3 days) disease.^[15] In the same study, presenteeism in the group with severe AD was 15%, and in the group with moderate AD 6%.^[15] Similar observations were also reported in Denmark, France and Spain.^[30, 31, 18] In Europe average annual indirect costs for a patient with severe AD are approximately 1.100 EUR, moderate 550 EUR and mild 150 EUR.^[18] In the UK, absence from work due to atopic dermatitis was estimated at 4 days, and in the case of severe disease - at 14.9 days per year (an average per AD patient).^[22, 23]

Disease control

The amount of indirect costs in AD is higher in the case of an uncontrolled form of the disease than in the case of a controlled disease.^[32, 20] For Polish patients with AD that do not respond to treatment, the average annual number of days spent on sick leave is 35, while for those who respond to treatment 10 days.^[33] Annual absenteeism costs calculated based on statistical and demographic data from ECONOMEDICA AZS 2018 study amount to 908 EUR for patients responding to treatment and 3.148 EUR for patients who do not respond to treatment.^[33] When presenteeism cost were included, total indirect costs amount to 4.900 EUR for patients responding to treatment and 12.700 EUR for patients who do not respond to treatment (Figure 3).^[1, 2, 33, 34]

LOSS OF PRODUCTIVITY DEPENDING ON THE TREATMENT RESPONSE



Change in loss of productivity after treatment



Figure 3. Loss of productivity depending on the treatment response

Type of treatment used

The use of ineffective treatment significantly increases the indirect costs of atopic dermatitis (Figure 4).^[35, 36] Compliance with medical recommendations, including the use of maintenance therapy, and adequate patient education can also significantly reduce indirect costs.^[37, 38, 39] With regard to the selection of optimal therapy, one should also pay attention to the fact that the type of AD treatment not only affects the amount of direct costs depending on the price of therapy, but also the amount of indirect costs, due to the time needed for the application of a given therapy.^[40]

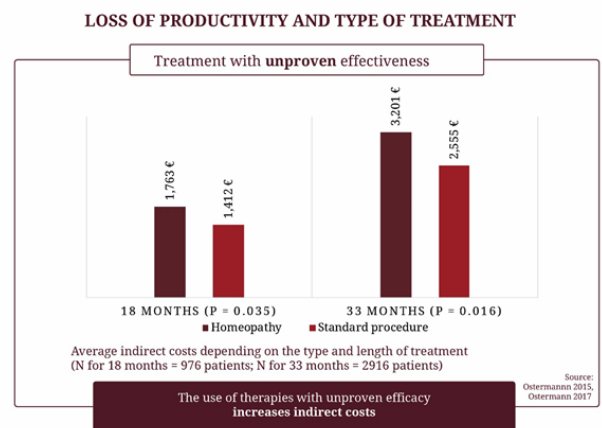


Figure 4. Loss of productivity and type of treatment (standard procedure – standard of care)

Conclusions

Atopic dermatitis is often underestimated due to the fact that it is a non-life-threatening condition. However, this disease negatively affects patients' quality of life, their psychological and social and professional relations, and the burden in QALY is higher than in diabetes or hypertension.^[22, 27] The publications found allow for the conclusion that a greater economic burden is associated with an increased incidence of AD and with the severity of the disease.. Since AD is a chronic skin disease that can occur at any age, and many treatments and prevention options exist, a high diversity of health economic findings can be expected. AD is associated with direct cost affecting payer, patient and patient's family and indirect cost due to absenteeism and presenteeism. Atopic dermatitis is a burden for the healthcare system and the state budget. It is estimated that around 10-20% of all dermatological visits are caused by atopic dermatitis. In addition, this disease generates high costs from a societal perspective, resulting from the

high prevalence of the disease and reduced productivity of employees with AD. Patients face persistent itching and pain in the affected areas and sleep disturbances, resulting in fatigue and increased presenteeism, as well as a sense of lack of control of the disease. In addition, the presence of unsightly skin lesions reduces patients' self-esteem, which is exacerbated by social stigmatization and, consequently, may lead to development of mental disorders. This applies in particular to patients with the most severe form of the disease, for whom current treatment has proved unsuccessful. Suicidal ideation in patients with atopic dermatitis occur seven fold more often than in the general population (14%^[9] (AD population polish study data) vs. 2%^[46] (WHO estimates)).

All of the above-mentioned factors also affect the professional life of patients with atopic dermatitis, and thus the patient's finances and, in the broad perspective, the whole country.

According to the information based on a systematic review, major factors with impact on the amount of indirect costs in patients with AD are effectiveness of treatment, disease control (appropriate maintenance therapy between successive exacerbations) and patient education on disease state and symptoms management. Loss of productivity in patients with atopic dermatitis is strongly correlated with the severity of the disease - it is twice as high in patients with severe disease compared to moderate. In Polish patients with AD who do not respond to treatment, they spend an average of 35 days on sick leave annually compared to 10 days among responders. Most patients with moderate-to-severe AD have long-term progressions with different patterns that can be chronic, intermittent, or seasonal. A drug therapy is indicated in most cases, a basic therapy with emollients is practically always necessary. The use of ineffective treatment significantly increases the indirect costs of atopic dermatitis. The patient needs extend beyond healing of skin changes and affect all areas of life. They include a large variety of individual goals such as cessation of itch, no pain, less side effects from treatment, better sleep, be less depressed, regaining capability, and long-term control of disease.^[42] Currently therapeutic options available in Poland are not sufficiently effective to provide disease control in all patient with AD, are characterized with adverse reactions, their use is limited in time and therefore their use will not bring savings in indirect costs in patients with severe AD.^[1, 2, 5, 33] Currently, dupilumab is the only registered therapeutic option for adult and adolescent patients with moderate to severe atopic dermatitis (ciclosporin is mainly used in adult severe patients). Dupilumab is included in current clinical guidelines and is recommended by clinical societies.^[41, 43] In the Simpson 2016^[3] clinical study, after 4 months of follow-up, dupilumab groups reported less loss of productivity, expressed as a lower average of days left

at school or work (0.5-2.1 days) relative to placebo (3.5 days). Available estimates indicate that treatment with dupilumab compared with the lack of its use will allow for savings in indirect costs of up to 30,400 EUR in one patient lifetime with severe AD (after taking into account the 5% discount rate).^[2]

It should be noted, however, that for patients with the highest degree of disease severity, access to effective, innovative therapies, that not only control the disease symptoms and improve the quality of life of patients with atopic dermatitis, but also affect overall patient productivity is of key importance. Such therapies include dupilumab - the first monoclonal antibody registered in the European Union in 2017 for the treatment of moderate to severe AD, which has been granted breakthrough status by the American Food and Drug Agency (FDA) and is the only dermatologic drug receiving an "innovative status" in Italy. Due to the difficult situation of Polish patients with severe AD, in whom previous treatments did not allow control of the disease, reimbursement of the above mentioned therapy provides an opportunity for effective and safe treatment and will decrease indirect costs.

Authors declare none potential conflicts of interest.

Supplementary material

This analysis was based on a systematic review of the literature. A systematic search in medical information databases (MEDLINE, Embase, ISPOR, Scopus, Web of Science, Google Scholar) was conducted on October 23, 2019, based on prepared search strategies. The verification at the level of titles and abstracts was carried out independently by two analysts, and reports considered useful by at least one of them were qualified for the next stage. Full-text publications were selected independently by two out of three analysts. In the case of disagreement of opinions as to the qualification of the research, the final position was agreed by consensus. The degree of compliance in the second stage was 100%. The selection of the studies in both phases was performed according to the inclusion criteria presented below.

As a result of the search, a total of 3,449 bibliographic items were found, additionally 1 work was provided by co-authors. After removing duplicates, 3,154 publications were included in further analysis. After the initial selection of titles and abstracts, 83 papers were qualified for further analysis based on the full texts, while the selection criteria were met by a total of 35 publications, the information of which was taken when preparing this article.

Inclusion criteria

Table 1. Inclusion and exclusion criteria

| Field | Inclusion criteria |
|--------------|---|
| Population | <ul style="list-style-type: none"> · adults and children 12 years of age and older with moderate to severe AD · Studies conducted in a wider than target population, ie studies conducted in a mixed population (children, adults), also including children under 12 years of age, were also eligible for the analysis. Studies conducted exclusively in the pediatric and Asian populations were excluded. |
| Intervention | Not valid |
| Comparator | Not valid |
| End points | <ul style="list-style-type: none"> · absentee endpoints (including: percentage and duration of missed working hours, dismissal and disability rates, costs), · presenteeism endpoints (including: percentage and length of lost time at work, costs), · loss of productivity endpoints (including: percentage and number (days / hours) of time lost productivity, costs) |
| Methods | <ul style="list-style-type: none"> · research regardless of the methodology (RCT, nRCT, RWD, cost-effectiveness analysis, economic models), · research published in Polish and English, · research published in full-text form (not applicable to Polish data) |

Search strategy

Table 2. Search strategy in MEDLINE (via Pubmed)

| No. | Keyword | Results |
|-----------------------------------|--|-----------|
| 1. | atopic dermatitis [MeSH] | 19 115 |
| 2. | atopic AND (dermatitides OR dermatitis OR neurodermatitis OR neurodermatitides OR eczema) | 28 285 |
| 3. | disseminated AND (neurodermatitis OR neurodermatitides) | 45 |
| 4. | #1 OR #2 OR #3 | 28 306 |
| 5. | indirect | 182 660 |
| 6. | cost OR costs OR expenditure OR expenditures OR (human AND capital) | 1 119 524 |
| 7. | #5 AND #6 | 17 268 |
| 8. | absenteeism OR presenteeism OR cost-of-illness OR economic burden OR “informal care” OR “informal caregiver” OR “informal caregiving” OR “family care” OR “family caregiver” OR “family caregiving” OR “burden of illness” OR expenditures OR “sick leave” OR “medical leave” OR “productivity” OR “disability” OR “household” OR time-off OR “days off” OR “cost of care” | 440 205 |
| 9. | Health expenditures [MeSH] | 21 284 |
| 10. | Cost of illness [MeSH] | 25 823 |
| 11. | “social consequences” | 2 624 |
| 12. | “social cost” OR “social costs” OR “societal cost” OR “societal costs” | 3 677 |
| 13. | #7 OR #8 OR #9 OR #10 OR #11 OR #12 | 456 525 |
| 14. | #4 AND #13 | 542 |
| Last search date: 23 October 2019 | | |

Table 3. Search strategy in Embase

| No. | Keyword | Results |
|-----------------------------------|---|---------|
| 1. | atopic AND ('dermatitis'/exp OR dermatitis) AND [embase]/lim | 43 117 |
| 2. | atopic AND (dermatitides OR dermatitis OR neurodermatitis OR neurodermatitides OR eczema) AND [embase]/lim | 43 355 |
| 3. | disseminated AND (neurodermatitis OR neurodermatitides) AND [embase]/lim | 31 |
| 4. | #1 OR #2 OR #3 | 43 545 |
| 5. | indirect AND [embase]/lim | 163 035 |
| 6. | (cost OR costs OR expenditure OR expenditures OR (human AND capital)) AND [embase]/lim | 827 774 |
| 7. | #5 AND #6 | 19 370 |
| 8. | ((absenteeism OR presenteeism OR 'cost of illness' OR economic) AND burden OR 'informal care' OR 'informal caregiver' OR 'informal caregiving' OR 'family care' OR 'family caregiver' OR 'family caregiving' OR 'burden of illness' OR expenditures OR 'sick leave' OR 'medical leave' OR 'productivity' OR 'disability' OR 'household' OR 'time off' OR 'days off' OR 'cost of care') AND [embase]/lim | 417 938 |
| 9. | ('health care cost'/exp OR 'health care cost') AND [embase]/lim | 241 905 |
| 10. | ('cost of illness'/exp OR 'cost of illness') AND [embase]/lim | 11 618 |
| 11. | 'social consequences' AND [embase]/lim | 2 568 |
| 12. | ('social cost' OR 'social costs' OR 'societal cost' OR 'societal costs') AND [embase]/lim | 4 111 |
| 13. | #7 OR #8 OR #9 OR #10 OR #11 OR #12 | 646 867 |
| 14. | #4 AND #13 | 1153 |
| Last search date: 23 October 2019 | | |

Table 4. Search strategy in other sources

| No. | Keyword | Results |
|-----------------------------------|--|---------|
| ISPOR | (atopic AND (dermatitides OR dermatitis OR neurodermatitis OR neurodermatitides OR eczema) AND ((indirect AND (cost OR costs OR expenditure OR expenditures OR (human AND capital))) OR (absenteeism OR presenteeism OR cost-of-illness OR economic burden OR "informal care" OR "informal caregiver" OR "informal caregiving" OR "family care" OR "family caregiver" OR "family caregiving" OR "burden of illness" OR expenditures OR "sick leave" OR "medical leave" OR "productivity" OR "disability" OR "household" OR time-off OR "days off" OR "cost of care" OR "health expenditures" OR "cost of illness" OR "social consequences" OR "social cost" OR "social costs" OR "societal cost" OR "societal costs")) | 55 |
| Scopus | TITLE-ABS-KEY ("atopic dermatitis" AND ("indirect costs" OR absenteeism OR presenteeism OR productivity)) | 135 |
| Web of Science | TOPIC: ((("atopic dermatitis" AND ("indirect costs" OR absenteeism OR presenteeism OR productivity))) | 94 |
| Google Scholar | "atopic dermatitis" AND "indirect costs" | 1470 |
| Last search date: 23 October 2019 | | |

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