

Title: Cost-of-illness of atopic dermatitis in Germany: Data from dermatology routine care

Running head: Cost-of-illness of atopic dermatitis in Germany

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Conflicts of interest

N Mohr reports that the institute has received unrestricted grants from Sanofi during the conduct of the study. Sanofi was not involved in study design, data collection, data analysis, interpretation of data, and writing of the paper.

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T Bieber was speaker, and/or consultant and/or investigator for AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Böhringer-Ingelheim, Celgene, Daichi-Sankyo, Dermavant/Roivant, DermTreat, DS Pharma, RAPT/FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, Kymab, LEO, Lilly, L'Oréal, MenloTx, Novartis, Pfizer, Pierre Fabre, Sanofi/Regeneron, UCB.

T Werfel has nothing to declare.

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M Augustin reports that the institute has received unrestricted grants from Sanofi during the conduct of the study. Sanofi was not involved in study design, data collection, data analysis, interpretation of data, and writing of the paper. Outside the submitted work he has served as consultant and/or paid speaker for and/or has received research grants and/or honoraries for consulting and/or scientific lectures for and/or got travel expenses reimbursed and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of atopic eczema including Almirall, ALK, Astellas, GSK, La Roche Posay, MSD, Sanofi Aventis, Stallergenes.

Summary

Background:

Progress in the management of atopic dermatitis (AD) and the recent introduction of the first biologic have raised interest in the costs of treating AD.

Objectives:

Since there is a lack of recent data, the objective of this study was to determine the annual costs of adults with AD from the societal perspective.

Methods:

A nationwide cross-sectional study was conducted in 112 dermatological practices offices under routine conditions. Cost parameters were collected with a standardised questionnaire on disease-related costs. This questionnaire allows the determination of costs for systemic and topical treatment, outpatient and inpatient visits, rehabilitation stays as well as travel costs. Direct costs were determined for the statutory health insurance (SHI) and for the patients (out-of-pocket costs). Societal costs also included the indirect costs due to incapacity to work. Costs were calculated for all severity and further stratified by mild and moderate-to-severe AD.

Results:

From August 2017 to June 2019, N = 1,291 adult patients from all over Germany were included. The total annual costs in the group with all severity grades (n = 706) amounted to € 3,616 ± € 6,452 (median € 874) per patient. For patients with mild AD (n = 367), the annual costs were € 1,466 ± € 3,029 (median € 551) per patient, while they were € 5,229 ± € 7,538 (median € 1,791) for patients with moderate-to-severe AD (n = 682). The total economic burden for treating adult patients with AD in Germany are estimated at more than € 2.2 billion.

Conclusions:

In total, the data from this study show that, compared to e.g. psoriasis, AD has a moderate level of costs-of-illness in Germany. The approval of new therapies is expected to lead to markedly more resource utilisation in the next years.

Key words: Atopic dermatitis; Cost-of-illness; Costs; Health Economics; Primary data

Introduction

Atopic dermatitis (AD) affects 2-4% of adults in Germany¹⁻³ and up to 7% worldwide.^{2,4,5} Various treatment needs make the therapy of AD challenging and despite receiving systemic therapy, patients still have unmet therapeutic needs also resulting in a substantial disease burden with impaired quality of life and profound work productivity loss.⁶⁻¹⁰ The European guidelines for treatment of AD recommend reactive topical therapy for mild AD (SCORing Atopic Dermatitis, SCORAD < 25) or transient eczema, complemented by UV therapy and proactive topical therapy for moderate AD (SCORAD 25-50) or recurrent eczema and systemic therapy and hospitalisation for severe AD (SCORAD > 50) or persistent eczema. Among the systemic therapies, dupilumab, the first biologic therapy, was approved as first-line treatment for moderate-to-severe AD in September 2017.^{11,12} Various studies have confirmed not only the high efficacy of dupilumab¹³⁻¹⁵ but also a favourable safety profile compared to classic immunosuppressive drugs.¹⁶⁻²⁰ Next to dupilumab, there are now further biologics and small molecules in phase II and phase III trials, which suggests that further developments in AD treatment are expected soon.^{21,22}

Not least due to these developments, interest in health economic research on AD increased in the last years, predominantly in the USA followed by Germany and the United Kingdom.²³ The most recent cost-of-illness (COI) analysis on AD included data from 2010 to 2015 collected in the USA and provided direct costs between US\$ 10,461 and US\$ 19,462 per patient.²⁴ In Germany, six COI studies on AD have been published between 1999 and 2010.²⁵⁻³⁰ Two of these studies provided both direct and indirect costs for adults.^{25,28} The most recent study was published in 2005 and found average annual total costs of € 1,425 per patient (both children and adults) with AD.²⁸ As there have been many changes in AD care since then, up-to-date data on the COI of AD are urgently needed. Therefore, the objective of this study was to determine the annual costs of adults with AD from the societal perspective.

Methods

Study design and patients

A nationwide cross-sectional study was conducted in Germany. Data collection was carried out in randomly selected dermatological practices offices between August 2017 and June 2019. These offices included office-based physicians as well as dermatological clinics. The dermatologists were asked to include patients sequentially as they show up in their practice office. Half of the practices offices were

asked to recruit patients with all grades of severity (in the following referred to as non-selected group). The other ones should only include patients with moderate-to-severe AD. The decision whether moderate-to-severe AD is present was based on the clinical judgement by the dermatologist. As an orientation, the following explanation was provided: ~~was defined as follows:~~ "A moderate to severe atopic dermatitis is present if the patient is suitable for a systemic therapy. (However, this does not have to be done immediately). Examples for this:

- Relevant clinical severity, for example global severity (PGA) 4 on a 5-level scale, BSA from 15%, SCORAD from 30 or EASI from 10
- High subjective disease burden (DLQI > 10) - Insufficient response to topical therapy attempts
- Particularly high degree of suffering due to visible or other sensitive areas (e.g. genitals)
- Other medical reasons, for example particular comorbidity
- Patient is already receiving systemic therapy for atopic dermatitis"

~~In order to verify the grade of severity~~ The unselected group was included because one of the research goals was to observe a representative sample of all patients with AD under dermatological care. In order to also be able to focus on patients with moderate-to-severe AD in a sufficient number for further subgroups analyses, we chose to additionally recruit patients only with moderate-to-severe AD. All physicians were asked to rate whether the patient is a candidate for systemic treatment at the end of the questionnaire. Patients who were recruited for the moderate-to-severe group but were not rated as candidates for systemic treatment were excluded due to implausible data. Patients from the non-selected group were further ~~The remaining ones were~~ categorised as *mild AD* (no candidate for systemic treatment) and *moderate-to-severe AD* (candidate for systemic treatment). This results in three groups that are reported in this paper (non-selected group, mild AD, moderate-to-severe AD; Fig. 1).

<<<Please insert Figure 1 here>>>

Patients were informed about the study by their dermatologist and signed an informed consent. For each patient, the dermatologist completed a questionnaire providing basic medical data. These data included the grade of severity according to SCORAD and the Investigator's Global Assessment (IGA, scale from 0 to 5), the Hanifin & Rajka criteria,³¹ comorbidity, and previous therapies. The patients also completed a questionnaire on their own. This questionnaire comprised questions on the sociodemographic status,

disease history, disease burden, applied therapies, quality of life (assessed with the Dermatology Life Quality Index, DLQI) and a standardised questionnaire on disease-related costs, as was already applied on a similar study on COI of psoriasis.³²

An ethics vote was obtained from the responsible ethics committee of the Medical Association of Hamburg (PV5463).

Cost determination

Cost parameters were collected with a standardised questionnaire on disease-related costs adapted for AD. This questionnaire allows the determination of the direct costs for systemic and topical treatment, outpatient and inpatient visits, rehabilitation stays as well as travel costs (Table 1). For each of these categories, patients reported their utilisation during the corresponding time periods. In case of systemic treatment, for example, they reported the name of the drug, the package size, and the number of packages purchased during the last three months. In the course of the data analysis, the costs for the respective packages were researched and extrapolated to twelve months. Missing or unclear data were replaced if possible, with plausible data for the respective case. Completely missing data in a cost category were replaced with zero € (= no utilisation) in case at least one question in the cost questionnaire was answered by the patient.

<<<Please insert Table 1 here>>>

Indirect costs were calculated using the human capital approach³⁸ based on the number of days unable to work that were indicated by the patients. The societal costs for one day absent from work was calculated according to the German recommendations for health economic evaluations³⁹ as $\frac{\text{total annual remuneration}}{\text{number of employees} * 365} =$ € 120.24. The maximum number of days absent from work was set at 230 days. Patients who claimed to be retired were excluded from the calculation of indirect costs and the costs were set to zero.

Statistical analysis

Data were entered from the paper-based questionnaires into a standardised Excel form. The first 100 questionnaires were entered twice in order to identify systematic errors. Statistical analyses were conducted using SPSS version 25 (IBM, Armonk, NY, USA). For the descriptive analysis standard measures (mean, median, standard deviation, minimum, maximum for continuous data and frequencies for categorical data) were used. Subgroup analyses were conducted using the non-parametric Mann-Whitney *U* test and the Kruskal-Wallis test.

Based on the cost data, the overall economic burden for Germany was calculated. For this purpose, the median costs were extrapolated to the total population, taking into account prevalence¹ and population size on 31.12.2018⁴⁰ in Germany. The costs for this calculation were derived solely from the non-selected group (all grades of severity).

Results

Sociodemographic data

A total of 1,692 dermatological practices offices randomly selected from a list of all office-based dermatologists in Germany were invited via mail to participate. Of those, 350 practices offices answered, 190 agreed to participate and 112 finally submitted completed questionnaires. From August 2017 to June 2019, N = 1,291 adult patients from all over Germany were included in total. Of those, n = 706 were recruited for the non-selected group including all grades of severity. Among those recruited for the group with only moderate-to-severe cases (n = 585), n = 233 were excluded due to missing or implausible information. Those cases were excluded from the total sample, resulting into n = 367 with mild AD and n = 682 with moderate-to-severe AD (Fig. 1, Table 2). In total, 56.5% were female (55.8% in the non-selected group; 66.8% in mild AD and 47.0% in moderate-to-severe AD).

Of the working patients (non-selected: n = 481 / 68.8%; mild AD: n = 246 / 67.4%; moderate-to-severe AD: n = 473 / 70.7%), 24.5% in the non-selected group, 16.1% in group mild AD and 34.1% in group moderate-to-severe AD stated that they had been unable to work at least one day in the past year due to AD.

<<<Please insert Table 2 here>>>

Costs of atopic dermatitis

The total costs amounted to € 3,616 ± € 6,452 (median € 874) per person and year in the non-selected group (Table 3). Considering the mean, systemic treatment caused the highest costs, followed by inpatient treatment. Male patients had significantly higher costs for outpatient treatment, resulting also in higher direct and total costs. Female patients had significantly higher costs for the consultation of alternative practitioners. The out-of-pocket costs borne by the patients amounted to € 377 ± € 497 (median € 211). The total costs for the statutory health insurance (SHI) were € 2,628 ± € 5,380 (median € 375) and were significantly higher for male patients.

<<<Please insert Table 3 here>>>

The total costs for patients with mild AD were € 1,466 ± € 3,029 (median € 551) per person and year (Table 4). Patients with moderate-to-severe AD had total costs of € 5,229 ± € 7,538 (median € 1,791). While the costs were highest for inpatient treatment followed by topical treatment among those with mild AD, systemic treatment was the greatest category in moderate-to-severe AD. Among the group with moderate-to-severe AD women had significantly higher costs for topical treatment, the consultation of alternative practitioners and also higher out-of-pocket costs.

<<<Please insert Table 4 here>>>

In the non-selected group, the total costs did not differ significantly between the different age groups (Table 5). SHI costs were highest for patients of 65 years and older in the non-selected group and in patients with moderate-to-severe AD (Table 6).

<<<Please insert Table 5 here>>>

<<<Please insert Table 6 here>>>

SHI costs were mainly driven by medication (topical, systemic and further reimbursed therapies; Fig. 2). In the non-selected group medication costs were significantly highest ($P = 0.006$) for patients of 65 years and older while they were highest for patients between 35 and 64 years among those with moderate-to-severe AD ($P = 0.027$).

<<<Please insert Figure 2 here>>>

Sensitivity analyses excluding patients receiving dupilumab ($n = 50$ in the non-selected group, $n = 78$ in moderate-to-severe AD) resulted in total costs of € 2,309 ± € 4,294 (median € 759) per patient and year in the non-selected group and in € 3,190 ± € 4,974 (median € 1,305) in moderate-to-severe AD. These differences were mainly driven by lower costs for systemic treatment. In the non-selected group these were € 260 ± € 1,410 (median € 0) when excluding patients receiving dupilumab compared to € 1,540 ± € 4,913 (median € 0). In moderate-to-severe AD costs for systemic treatment were € 444 ± € 1,663 (median € 0) for patients without dupilumab (compared to € 2,530 ± € 6,096, median € 0 without exclusions).

Overall economic burden

Assuming a prevalence of 3.7% in the German adult population, the costs per year for treating adults with AD amount to € 2,226,580,9473, i.e. more than € 2.2 billion (Table 7).

<<<Please insert Table 7 here>>>

Discussion

This study aimed at characterising the cost-of-illness for atopic dermatitis in Germany. This research question is of considerable relevance since AD is a very common and burdensome disease and the last available data for Germany date back to 2005.²⁸ Thus, a representative nationwide update on costs from the societal perspective was intended. Since the data were obtained from primary evaluations on patient level, they can be related to clinical and patient-reported information, which is not available in secondary data analyses from the statutory health insurances.

The baseline data indicated that the clinical and patient-reported profiles largely resemble a prior study on health care for AD in 2014.⁴¹ Thus, the average level of disease burden has not decreased in the consecutive period of 5 years.

The costs reported in this study are only those costs that can be attributed directly to AD. Costs that arise due to the numerous comorbidities of patients with AD^{1,3,42,43} are therefore not included.

The calculated COI of AD in Germany amounted to € 3,616 ± € 6,452 (median € 874) per person and year in the non-selected group. Due to the random recruitment of dermatology practices offices and clinics all over Germany and the non-selective recruitment of patients, this group can be considered as broadly representative for adult patients with AD in dermatological care in Germany. As expected, the costs for more severe disease were significantly higher, both in terms of treatment costs as well as indirect costs. Regarding age, there was a trend to higher treatment costs in the elderly whereas indirect costs accounted most in younger persons which is related to the occupation status.

The most recent comparable study from Germany was published in 2005 and reported total costs of € 1,425 per patient.²⁸ However, this study included both children and adults, limiting the comparability to our data. Nevertheless, the more than doubling of total costs is remarkable. It is assumed that especially costs for systemic treatment have increased since then due to the introduction of new treatments. They now constitute the largest volume of costs, followed by hospital costs and topical treatment.

The estimated total annual costs for AD in Germany in our study reached € 2.2 billion which is markedly higher than these costs in 2005 (€ 1.6 billion). Applying the annual inflation rate for Germany⁴⁴ to the overall burden from 2005 results in annual costs for AD of € 2.0 billion in 2019. These are still lower than the costs we calculated, though in the latter study from 2005 also children were included. This suggests a markedly higher overall cost burden from AD in Germany in the current study.

In this study, indirect costs of annually € 483 per year due to incapacity to work were calculated. For this calculation we applied the human capital approach, which neglects whether the work is taken over by others. However, especially in case of short-term absences from work, as can be assumed in AD, the work is often done by others or by the employees themselves after their return.

Comparability of COI studies across countries may be difficult due to different health systems. Even comparisons within Germany may be limited due to different methods of cost determination or differing target populations. For this, further international comparisons should be taken with caution. However,

there were apparently higher COI in AD in the USA and lower costs in several other countries, reflecting again particularities in the health systems.²³

The distribution of the cost data in the current study is mainly right skewed with median values that are much lower than mean values. While the median is the most common value, the mean is more sensitive to outliers. A right skewed distribution therefore indicates that the highest costs are caused by few patients with very expensive treatment. This is also shown by the sensitivity analysis, in which the mean values changed significantly when dupilumab was excluded, while the median values remained largely stable. However, even when excluding dupilumab the distribution remains right skewed, which indicates that there are additional cost drivers. In order to analyse this comprehensively numerous parameters as severity, quality of life, subjective satisfaction with therapy, therapies in the past and further factors need to be considered in future analyses.

The cross-sectional study design comes along with methodological peculiarities that should be taken into account when interpreting the data. The cost data were collected retrospectively and are therefore prone to recall bias. To reduce this bias, we varied the recall period as illustrated in Table 1. While less common events as hospitalisation were asked for the last twelve months, the more detailed information such as medication was asked for the last three months. Extrapolation of these data to the last year may lead to an overestimation in case some therapies were only used for a short time. At the same time, however, patients may have received fewer medications in the three months of the recall period than before, so that these effects may outweigh each other. The cross-sectional design also implies that the severity measured at the time of data collection may not necessarily be associated with the costs generated in the previous year. We have therefore based the classification of severity on the physician's assessment of whether a patient is a candidate for systemic therapy rather than on the measured SCORAD. Doing this, we also account for the necessity to also take further criteria into account such as quality of life impairment,²¹ which is also discussed in the new German guideline on systemic treatment in AD.⁴⁵ The results of this study, including the high number of implausible cases in the moderate-to-severe group, indicate that there is a marked disparity between the definition of eligibility for systemic treatment, the actual use of systemic treatment in these patients, and the clinical characterization of the patients by SCORAD and DLQI as being severe. An analysis of the dermatologist' decision process on the indication for systemic treatment could contribute to discussions on appropriate severity strata for AD.

When interpolating the study results to the overall population in Germany, we calculated the costs from the societal perspective. Doing this, we assumed all patients to be covered by the SHI. However, 2.2% in

our study population and about 10% of the total German population are privately insured. For these, there may be a limitation of relating the outcomes of this study to the privately insured persons.

A particular advantage of using primary data is the consideration of out-of-pocket costs. Compared to a methodologically similar study for psoriasis,³² these were considerably higher for AD (Fig. 3). This may be explained by two major effects: 1) there are less effective reimbursed treatment options in AD compared to psoriasis, 2) there is a generally higher need in AD to use topical basic emollients which are not reimbursed, both resulting in higher self-paid purchases of emollients. The marked financial burden of patients with AD was also subject of other published studies in which annual out-of-pocket costs up to € 927 were determined.^{46–48} The further investigation of patient-related costs is an important research topic for the future, also against the background of equity considerations.

<<<Please insert Figure 3 here>>>

The comparison of total drug costs reveals much higher expenses by the payers for psoriasis than for AD. This largely reflects the large number of guideline-compliant drugs for psoriasis whereas in AD the treatment options are much more restricted. In particular, there has been a marked and still ongoing increase in systemic treatment for psoriasis, which is not yet true for AD. The impact of these developments on costs and patient benefit was recently examined.⁴⁹ While the management of moderate-to-severe AD will doubtlessly improve as well with newly approved therapies such as dupilumab and others, this will be accompanied by significantly higher drug costs for patients with AD.

In total, the data from this study show that AD has a moderate level of costs-of-illness in Germany but indicates a trend to markedly more resource utilisation in the next years. Further studies should focus on the question of balance between costs and benefits both on an individual and on a societal level.

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Tables

Table 1 Cost categories considered for the direct costs: payer, recall period, assumptions and sources used for cost determination

Cost category	Payer		Recall period	Explanations, assumptions and data sources
	SHI	Patient		
Topical treatment	x	x	Last three months	• Differentiation between prescription pharmaceuticals, over the counter products and freely available products
Systemic treatment				• Consideration of the pharmacy sales price, manufacturer selling price and patient copayments obtained from German “Lauer-Taxe”³¹ (standard reference guide for all pharmaceuticals, medical devices and aids) • Mixed price from two drug stores for freely available products
Further reimbursed therapies	x		Last three months	• UV therapy • Psychotherapy, differentiation between single and group therapy • Costs obtained from the fee schedule of the German National Association of SHI physicians³²
Inpatient treatment	x	x	Last twelve months	• Hospital stays: ○ Relative costs weight of 0.699 determined with web-based diagnosis-related groups (DRG) grouper³³ using the international classification of diseases (ICD) L20.8, L20.9, L28.0 multiplied with the base case value for 2019 of € 3,544.97³⁴ ○ Mean length of stay: 6 days ○ Patient copayment of € 10 per day for a maximum of 28 days • Rehabilitation stays: ○ Mean length of stay: 24 days ○ Patient copayment of € 10 per day ○ SHI costs of € 128.05 per day

			○ Data obtained from the fee schedule of rehabilitation payers • Day-care hospital: ○ SHI costs of € 220 per day (mixed price from 10 day-care hospitals)
Outpatient treatment	x	Last twelve months	• Number of consultations indicated by the patient per quarter and specialisation of the physician • Physician's fees obtained from the National Association of SHI Physicians³⁵
Travel costs	x	Last twelve months	• Distance and costs indicated by the patient • In case no costs were indicated, € 0.30 per kilometre were assumed
Alternative practitioners/naturopaths	x	Last twelve months	• Mean of the costs indicated by patients in free text entries, maximum of € 650 per year

SHI, statutory health insurance.

References: ³¹CGM Lauer, ³²KBV Kassenärztliche Bundesvereinigung, ³³DRG-Research Group Webgrouper, ³⁴GKV-Spitzenverband, ³⁵KBV Kassenärztliche Bundesvereinigung.

Table 2 Sociodemographic and disease specific data of the included patients

	Non-selected group (n = 706)				Mild AD (n = 367)				Moderate-to-severe AD (n = 682)			
	n	Mean	Median	SD	n	Mean	Median	SD	n	Mean	Median	SD
Age	703	41.1	38	16.2	366	39.0	34.0	16.3	679	42.9	42.0	15.5
BMI	701	26.1	24.7	7.8	364	25.8	24.5	5.3	673	26.2	25.0	7.6
Years since diagnosis	625	27.9	27.0	16.4	323	24.1	23.0	15.7	607	31.0	30.0	16.2
SCORAD	671	45.4	44.8	20.6	351	38.3	38.5	17.2	635	57.2	59.0	18.9
IGA	688	2.8	3.0	1.1	361	2.4	3.0	1.0	656	3.5	4.0	1.1
DLQI	702	8.5	7.0	6.5	364	7.4	6.0	5.8	678	10.7	10.0	7.0
Days unable to work in the past year*	462	5.6	0.0	20.4	236	2.9	0.0	16.2	446	8.4	0.0	23.9
	n	%			n	%			n	%		
SCORAD $\geq$ 30	502	74.8			230	65.5			579	91.2		
IGA $\geq$ 4	189	27.5			33	9.1			354	54.0		
DLQI > 10	222	31.6			86	23.6			308	45.4		

AD, atopic dermatitis; BMI, body mass index; SCORAD, SCORing Atopic Dermatitis; IGA, Investigator's Global Assessment; DLQI, Dermatology Life Quality Index.

*only employed patients.

Table 3 Total annual costs [€] of atopic dermatitis per patient and year from the societal perspective in the non-selected group

Cost category	Group	Mean	Median	SD	Min	Max	P-value
Topical treatment	Total	488	317	604	0	6,577	0.567
	Male	522	328	646	0	5,087	
	Female	467	312	582	0	6,577	
Systemic treatment	Total	1,540	0	4,913	0	25,977	0.833
	Male	2,025	0	5,651	0	24,661	
	Female	1,055	0	4,059	0	25,977	
Further reimbursed therapies	Total	238	0	1,493	0	29,934	0.944
	Male	153	0	821	0	8,125	
	Female	302	0	1,886	0	29,934	
Inpatient treatment	Total	631	0	1,848	0	17,844	0.218
	Male	717	0	1,981	0	16,653	
	Female	522	0	1,669	0	17,844	
Outpatient treatment	Total	139	118	104	0	633	< 0.001
	Male	152	146	103	0	555	
	Female	128	107	104	0	633	
Travel costs	Total	57	13	172	0	2,985	0.119
	Male	58	17	125	0	1,260	
	Female	56	12	205	0	2,985	
Alternative practitioners/naturopaths	Total	40	0	125	0	650	0.012
	Male	28	0	107	0	650	
	Female	52	0	140	0	650	
Out-of-pocket costs	Total	377	211	497	0	4,777	0.131
	Male	350	188	464	0	2,788	
	Female	395	232	527	0	4,777	
SHI costs	Total	2,628	375	5,380	0	36,218	< 0.001
	Male	3,146	478	5,855	0	30,753	
	Female	2,088	312	4,797	0	36,218	
Direct costs	Total	3,133	754	5,754	0	38,642	0.020

	Male	3,655	869	6,280	0	32,981	
	Female	2,582	676	5,116	0	38,642	
Indirect costs	Total	483	0	2,058	0	27,655	
	Male	568	0	2,137	0	27,655	0.156
	Female	422	0	2,046	0	27,655	
Total costs	Total	3,616	874	6,452	0	45,255	
	Male	4,223	1,079	6,945	0	37,193	0.007
	Female	3,004	763	5,884	0	45,255	

P-value, significance of difference between male and female according to Mann-Whitney *U* test; SHI, statutory health insurance.

Total n = 706, male: n = 301, female n = 380.

Table 4 Total annual costs [€] of atopic dermatitis per patient and year from the societal perspective stratified by severity

Cost category	Group	Mild AD (n = 367)						Moderate-to-severe AD (n = 682)					
		Mean	Median	SD	Min	Max	<i>P</i> -value	Mean	Median	SD	Min	Max	<i>P</i> -value
Topical treatment	Total	377	267	471	0	5,087		557	379	649	0	6,577	
	Male	406	263	587	0	5,087	0.725	533	335	655	0	5,060	0.014
	Female	362	272	409	0	2,850		597	418	662	0	6,577	
Systemic treatment	Total	48	0	214	0	3,040		2,530	0	6,096	0	29,471	
	Male	84	0	358	0	3,040	0.717	2,657	0	6,314	0	29,471	0.063
	Female	31	0	80	0	508		2,350	41	5,853	0	25,977	
Further reimbursed therapies	Total	119	0	658	0	5,897		288	0	1,687	0	29,934	
	Male	110	0	605	0	4,789	0.548	116	0	695	0	8,125	0.074
	Female	126	0	700	0	5,897		474	0	2,369	0	29,934	
Inpatient treatment	Total	486	0	1,696	0	17,844		839	0	2,074	0	22,301	
	Male	458	0	1,403	0	10,780	0.670	1,032	0	2,460	0	22,301	0.082
	Female	486	0	1,819	0	17,844		604	0	1,459	0	10,507	
Outpatient treatment	Total	107	78	88	0	497		160	146	106	0	701	
	Male	118	107	86	0	458	0.027	158	146	104	0	701	0.824
	Female	102	78	90	0	497		160	146	105	0	633	
Travel costs	Total	42	8	142	0	1,728	0.148	66	18	189	0	2,985	0.528

	Male	49	10	140	0	1,260		68	17	181	0	2,520	
	Female	39	6	146	0	1,728		62	22	198	0	2,985	
Alternative practitioners/naturopaths	Total	36	0	115	0	650		33	0	112	0	650	
	Male	25	0	95	0	650	0.205	24	0	96	0	650	0.013
	Female	43	0	127	0	650		44	0	126	0	650	
Out-of-pocket costs	Total	290	150	391	0	3,021		418	262	521	0	4,777	
	Male	274	135	376	0	2,093	0.547	372	226	484	0	3,860	0.000
	Female	297	158	401	0	3,021		469	305	554	0	4,777	
SHI costs	Total	891	254	1,946	0	16,730		3,862	664	6,365	0	36,218	
	Male	940	306	1,875	0	15,741	0.040	4,018	696	6,480	0	30,753	0.665
	Female	862	223	1,994	0	16,730		3,640	630	6,220	0	36,218	
Direct costs	Total	1,215	509	2,127	0	18,139		4,473	1,221	6,784	0	38,642	
	Male	1,250	573	2,012	0	16,313	0.175	4,589	1,205	6,945	0	33,256	0.367
	Female	1,191	479	2,196	0	18,139		4,291	1,225	6,584	0	38,642	
Indirect costs	Total	252	0	1,613	0	27,655		756	0	2,618	0	27,655	
	Male	211	0	780	0	6,012	0.312	744	0	2,610	0	27,655	0.586
	Female	248	0	1,929	0	27,655		791	0	2,716	0	27,655	
Total costs	Total	1,466	551	3,029	0	35,053		5,229	1,791	7,538	0	45,255	
	Male	1,461	606	2,309	0	18,117	0.135	5,333	1,756	7,761	0	37,193	0.372

Female	1,468	516	3,377	0	35,053	5,082	1,781	7,308	0	45,255
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AD, atopic dermatitis; *P*-value, significance of difference between male and female according to Mann-Whitney *U* test; SHI, statutory health insurance.

Mild AD: male: n = 118, female n = 237; moderate-to-severe AD: male: n = 347, female n = 308.

Table 5 Total annual costs [€] of atopic dermatitis per patient and year from the societal perspective stratified by age in the non-selected group

Cost category	Age group	Mean	Median	SD	Min	Max	<i>P</i> -value
Out-of-pocket costs	18-34	398	204	526	0	3,610	0.241
	35-64	361	234	423	0	3,021	
	65+	354	168	665	0	4,777	
SHI costs	18-34	2,207	334	5,140	0	36,218	0.005
	35-64	2,899	444	5,521	0	30,753	
	65+	3,256	372	5,761	39	21,445	
Direct costs	18-34	2,710	658	5,513	0	38,642	0.034
	35-64	3,405	873	5,873	0	32,981	
	65+	3,775	624	6,259	39	23,772	
Indirect costs	18-34	597	2,479	0	0	27,655	< 0.001
	35-64	483	1,825	0	0	18,156	
	65+	0	0	0	0	0	
Total costs	18-34	3,307	6,480	783	0	45,255	0.092
	35-64	3,887	6,495	985	0	33,221	
	65+	3,775	6,259	624	39	23,772	

P-value, significance of difference between age groups according to Kruskal-Wallis test; SHI, statutory health insurance.

Age 18-34 n = 308, age 35-64 n = 325, age 65+ n = 70.

Table 6 Total annual costs [€] of atopic dermatitis per patient and year from the societal perspective stratified by age and severity

Cost category	Age group	Mild AD			Moderate-to-severe AD								
		Mean	Median	SD	Min	Max	<i>P</i> -value	Mean	Median	SD	Min	Max	<i>P</i> -value
Out-of-pocket costs	18-34	306	144	430	0	2,198		448	262	556	0	3,610	
	35-64	299	181	371	0	3,021	0.277	395	263	461	0	3,860	0.729
	65+	167	124	164	0	677		430	252	681	0	4,777	
SHI costs	18-34	789	202	1,565	0	12,967		3,318	475	6,172	0	36,218	
	35-64	1,065	285	2,423	0	16,730	0.138	4,191	745	6,577	0	30,753	0.021
	65+	692	286	1,352	39	5,742		4,234	773	5,971	0	21,445	
Direct costs	18-34	1,127	449	1,804	0	13,462		3,921	1,153	6,579	0	38,642	
	35-64	1,400	531	2,573	0	18,139	0.177	4,803	1,338	6,995	0	33,256	0.107
	65+	893	536	1,441	39	6,331		4,876	1,449	6,456	0	23,772	
Indirect costs	18-34	352	0	2,155	0	27,655		787	0	2,302	0	27,655	
	35-64	180	0	771	0	7,214	0.081	883	0	3,028	0	27,655	< 0.001
	65+	0	0	0	0	0		0	0	0	0	0	
Total costs	18-34	1,479	530	3,251	0	35,053		4,706	1,816	7,319	0	45,255	
	35-64	1,580	606	2,993	0	19,713	0.235	5,686	1,831	7,882	0	36,619	0.369
	65+	893	536	1,441	39	6,331		4,876	1,449	6,456	0	23,772	

AD, atopic dermatitis; *P*-value, significance of difference between age groups according to Kruskal-Wallis test; SHI, statutory health insurance.

Mild AD: age 18-34 n = 186, age 35-64 n = 149, age 65+ n = 31; moderate-to-severe AD: age 18-34 n = 252, age 35-64 n = 360, age 65+ n = 67.

Table 7 Estimation of the total economic burden in Germany

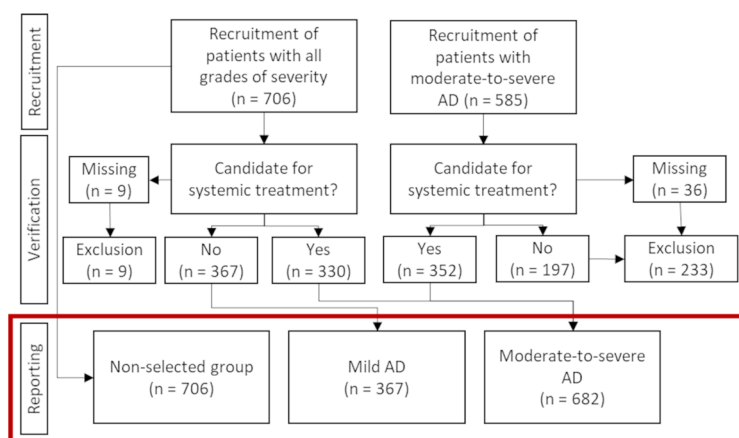
Group	Number of inhabitants ³⁸	Prevalence ¹ [%]	Number of affected persons in Germany	Costs per year and patient [median, €]	Costs per year [€]
18-19 years	1,696,864	6.6	112,163	556	62,318,724
20-29 years	9,800,607	5.4	527,273	758	399,778,128
30-39 years	10,646,445	3.9	409,888	903	370,288,840
40-49 years	10,426,257	3.3	351,365	1,137	399,449,142
50-59 years	13,474,166	3.0	404,225	959	387,667,925
60-69 years	10,302,411	2.9	294,649	745	219,501,685
70-79 years	7,685,929	2.7	208,289	627	130,549,093
> 80 years	5,389,106	2.4	129,339	533	68,929,684
Total (> 18 years)	69,421,785	3.7	2,547,780	874	2,226,580,947

Figure Legends

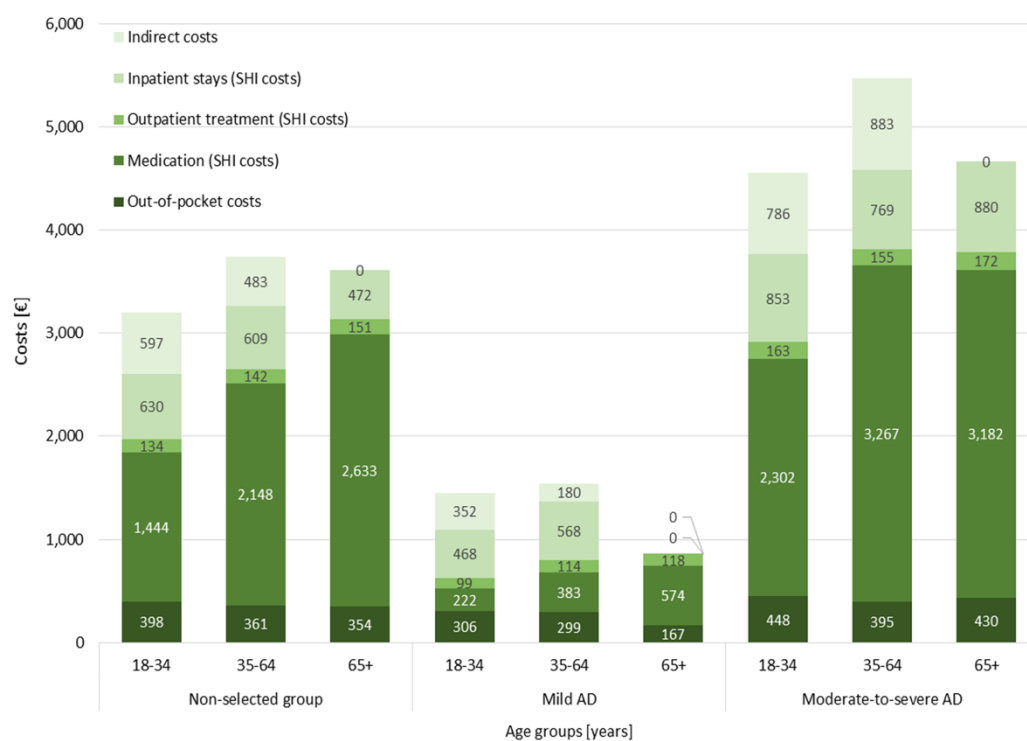
Figure 1. Flow chart of patient recruitment and formation of subgroups

Figure 2. Mean costs stratified by age groups, non-selected group: 18-34 (n = 308), 35-64 (n = 325), 65+ (n = 70); mild AD: 18-34 (n = 186), 35-64 (n = 149), 65+ (n = 31); moderate-to-severe AD: 18-34 (n = 252), 35-64 (n = 360), 65+ (n = 67)

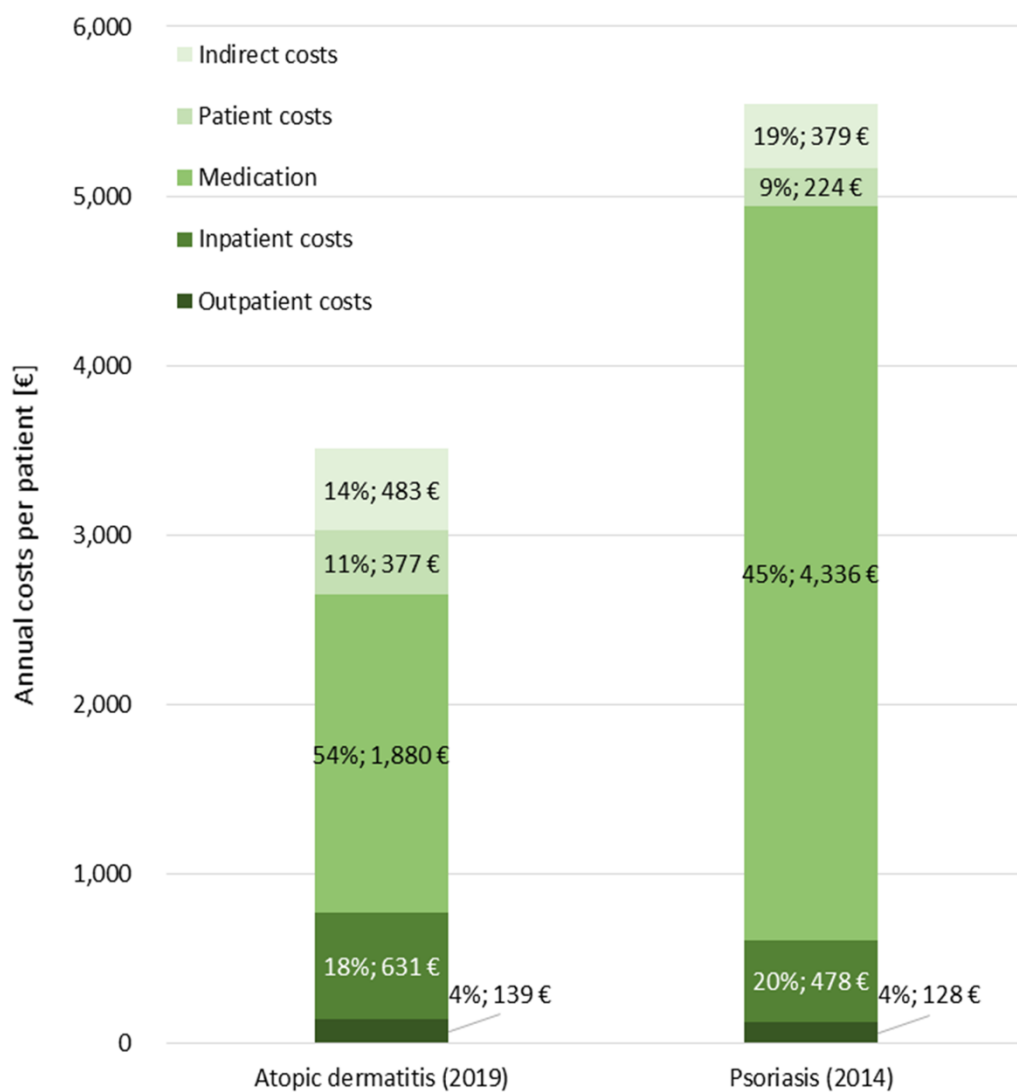
Figure 3. Comparison of cost distribution between atopic dermatitis (current study) and psoriasis³⁰



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