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Societal economic burden and determinants of costs for atopic dermatitis

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Abstract

Background: Atopic dermatitis (AD) is a common inflammatory skin disease while the economic burden of AD by severity is not adequately understood.

Objective: To estimate the societal economic burden and to identify cost determinants of AD.

Methods: In this population-based, controlled cohort study in Sweden, patients with AD were identified through diagnosis codes in primary or secondary care or by dispensed medications using administrative healthcare registers. A reference cohort without AD was randomly selected from the general population. Healthcare costs (primary/secondary care visits and dispensed medication) and indirect costs (care for sick children and long-term sick leave for adults) were calculated annually. AD patients were stratified by age (paediatric [age < 12], adolescent [12 ≤ age < 18] or adult [age ≥ 18]), and severity (mild-to-moderate [M2M] or severe AD) and matched to the reference cohort.

Results: Compared with controls, the annual mean per-patient direct healthcare costs in the first year following diagnosis were €941 and €1259 higher in paediatric patients with M2M and severe AD, respectively. In the first year following diagnosis, the mean indirect cost for care of sick children was €69 and €78 higher per patient in M2M and severe AD, respectively. In adolescents with M2M and severe AD, direct healthcare costs were €816 and €1260 higher, respectively. In adults, healthcare costs were €1583 and €2963 higher in patients with M2M and severe AD, respectively and indirect costs were €148 and €263 higher compared with controls. Management of comorbid medical conditions was an important driver of incremental healthcare costs. Total incremental societal economic burden for AD was €351 and €96 million

higher in patients with M2M and severe AD, respectively, compared to controls.

Conclusion: AD is associated with a significant societal economic burden primarily driven by the cost burden of M2M AD due to the high prevalence of this population. Regardless of severity level, management of non-AD comorbidities is a major driver of total costs.

KEYWORDS

atopic dermatitis, economic burden, eczema, epidemiology, healthcare costs, indirect costs, public health research

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease characterized by dry skin, pruritus and eczematous lesions, and is the most prevalent type of eczema.[1,2] Patients with severe AD oftentimes have more intense symptoms and a larger area of the body affected compared to patients with mild or moderate AD. This disease causes significant patient and family burden, impacting both costs[3,4] and quality of life.[5] In Western countries, including Sweden, approximately 15%–20% of children and 2%–10% of adults are affected by AD.[6–9] In 60%–80% of cases, the disease manifests during the first years of life but may start at any age.[6,10,11] It was traditionally believed that the disease gradually resolves in the majority of paediatric and adolescent patients when they enter adulthood, but in some patients, the condition persists and continues to have an impact on patients' well-being in adulthood and AD can also develop for the first time in adulthood.[6,7,12] A Danish study with long follow-up found that 67% of patients had disease activity 10 years after diagnosis. A Swedish study on the persistence of AD with a follow-up between 24 and 38 years also showed that as many as 59% of patients had AD at follow-up which indicates that AD patients continued to require healthcare long time after diagnosis.[13,14]

AD is associated with a considerable economic burden.[15] Healthcare costs generally increase with more severe disease,[16,17] but the economic burden of patients with mild-to-moderate (M2M) disease is also significant.[18] Moreover, out-of-pocket expenditures for affected individuals are substantial in AD. A European study found that adults with severe AD spend on average €927 per year on AD treatment. Moreover, 57% of patients with severe AD miss at least one day of work or school per year due to their disease.[19] In Europe, the direct per-patient cost per year of AD is estimated to be between €194–900 for mild AD and €417–20,695 for severe AD.[3,16,20,21] Additionally, indirect costs have been shown to comprise most of the total cost burden of AD in some settings[21] and a minority in others.[16] In general, differences in study design and the types of costs included have likely contributed to the large variations in outcomes observed in these studies.

Despite the considerable impact AD has on patients and families and recent increases in the prevalence of AD,[1] the economic burden of AD and patient-level cost drivers have not been extensively evaluated. Few studies include both children and adults with varying severity of their AD and may lack the generalizability and validity that population-based studies offer.[22,23] Moreover, while the impact of AD on patients' sick leave has been studied previously, no study to date has estimated the cost of parental care for sick children with AD.

The objective of this study was to estimate the societal economic burden of AD, defined as direct and indirect costs and determinants of these costs, in comparison to a matched reference cohort without AD.

MATERIAL AND METHODS

Data sources and ethics

In this study, data were extracted from five nationwide registries: the National Patient Register (NPR), the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Social Insurance Register (SIR) and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), and from two regional primary care databases (Västra Götaland Region [VEGA] and Skåne Region [RSVD]) covering approximately 1/3 of the Swedish population. Data were collected from 1 July 2005 (start of PDR) to 31 December 2018 (last available date of data from RSVD). The NPR

contains medical information for all in- and out-patient specialist (secondary care) contacts, including ICD-10 codes and dates. The PDR includes data on all pharmacy-dispensed medications from both primary and secondary care, including medications (Anatomical Therapeutic Chemical [ATC]-codes) and pharmacy dispensation dates. The CDR contains information on the date of death. The two primary care databases include data on diagnoses codes (International Classification of Diseases [ICD]-10) and corresponding dates for visits. The SIR includes information on government-paid long-term sick leave compensation (payment beginning after 2 weeks of consecutive days of sick leave) and government-paid compensation to parents to care for ill children under age 12 (payment beginning on the first day of the illness). The LISA contains demographic information including disposable household income, highest level of education achieved, current and past employment status and information about emigration from Sweden. Additionally, the Total Population Registry, which covers the entire Swedish population, was used to identify a reference cohort as well as parents of children to the AD- and the reference cohorts.

Inclusion in the Swedish healthcare registries used in this study is mandatory, thereby enabling nationwide coverage, extraction and analysis of secondary healthcare data. Primary care data was available regionally. Unique personal identification numbers, assigned to all Swedish citizens at birth or upon the date of immigration into Sweden, were used to link the data from each registry at the patient level. Ethics approval for the present study was obtained in July 2019 by the Swedish Ethical Review Board (reference number 2019-03840). Individual patient consent was not required according to local law regarding the collection of administrative secondary registry data.

Study population and study design

A cohort of patients with AD identified during 2007–2017 (inclusive) was included in this study. A validated case-finding AD algorithm in paediatric and adolescent patients, based on the diagnosis of AD (ICD-10: L20+), dispensation of topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) was employed to identify paediatric and adolescent patients with AD.[24] The use of this AD case-finding algorithm enabled us to identify paediatric and adolescent patients with AD managed in primary care (but who were not captured in the two regional primary care databases accessed) since the PDR covers medications prescribed in both primary and secondary care. The sensitivity and positive predictive value of this algorithm was low in adults (≥18 years of age) with AD. Therefore, adults were required to have at least one registered diagnosis of AD in primary or secondary care to be included in the adult AD-cohort in the present study. Since no case-finding algorithm is completely accurate, and to verify the robustness of the estimates in the paediatric and adolescent cohorts of this study, a sensitivity analysis in which paediatric and adolescent patients were identified exclusively using a registered diagnosis of AD (L20+) in primary or secondary care was conducted.

The date of the first AD diagnosis or dispensation of either a TCS or TCI during the study period was defined as the index date, that is, start date of follow-up. The study population was stratified into three groups based on the age at index date: paediatric AD cohort (age < 12), adolescent AD cohort (age ≥ 12 to <18) or adult AD cohort (age ≥ 18). The inclusion period was from 1 January 2007 to 31 December 2017, to enable at least 18 months of possible look-back and 12 months of possible follow-up for all individuals. Individuals were censored at death or emigration. Moreover, paediatric individuals were censored when they entered adolescence and adolescent individuals were censored when they entered adulthood. Patients were not allowed to re-enter the study in a different age group. This study used the European classification system for recording the potency of TCSs.[25]

Disease severity

Baseline severity was defined according to the type of dispensed AD-treatment (i.e., TCS, TCI, dupilumab, systemic immunosuppressants, systemic corticosteroids prescribed by a dermatologist and phototherapy) and the number of healthcare visits that a patient had with an AD-diagnosis in the 365 days before index to 30 days after index, as outlined in Table 1. Dispensation of systemic treatment was assumed to indicate severe AD in all three age groups following European treatment guidelines.[8,26] Dupilumab is since 2018 been reimbursed for patients with severe AD in Sweden.[27] Dispensation of potent or very potent TCSs was assumed to indicate severe AD in paediatric patients since it is only recommended to be used when milder TCSs have failed to provide a therapeutic effect. Conservative use of potent TCSs is also recommended in adolescent patients, but since some patients in their later adolescent years may be treated as adults, two (or more) dispensations of potent TCSs were required to indicate severe AD in this age cohort. In adult patients, very potent TCSs indicated severe AD. In paediatric and adolescent patients, a

TABLE 1 Algorithm to classify AD severity

	Paediatric and adolescent AD patients	Adult AD patients
Severe AD	• At least one dispensation of potent[a] or very potent TCS, dupilumab, systemic immunosuppressant treatment or systemic corticosteroids prescribed by a dermatologist • At least two secondary care visits with an AD-diagnosis as principal • At least one procedure of phototherapy in secondary care	• At least one dispensation of very potent TCS, dupilumab, systemic immunosuppressant treatment or systemic corticosteroids prescribed by a dermatologist • At least one procedure of phototherapy in secondary care
Mild-to-moderate AD	• At least one dispensation of mild or moderate TCS, TCI or emollients • At least one primary care visit with an AD-diagnosis (principal or secondary diagnosis) • At least one procedure of phototherapy in primary care • No more than one secondary care visit with an AD-diagnosis as principal diagnosis • One or more secondary care visit with an AD-diagnosis as secondary diagnosis	• At least one dispensation of mild, moderate or potent TCS, TCI or emollients • One or more primary or secondary care visit with an AD-diagnosis (principal or secondary diagnosis) • Phototherapy in primary care

Note: Given the inclusion criteria (AD-diagnosis or TCS/TCI dispensation), all patients were classified as either mild-to-moderate AD or severe AD.

Abbreviations: AD, atopic dermatitis; TCIs, topical calcineurin inhibitors; TCS, topical corticosteroid.

[a]Adolescent patients were required to receive two dispensations of potent TCSs within 90 days to be classified as severe AD. Patients were only required to meet one of the criteria in severe AD to be classified as severe AD. See Supporting Information: Tables S1 and S2 for ATC-code and profession code.

second visit to secondary care, potentially indicating that symptoms did not remit, was also regarded as severe AD. Severity was fixed throughout the follow-up period.

Reference cohort and matching

The reference cohort was randomly selected from the Swedish population and was comprised of individuals who did not have an AD-diagnosis and were not dispensed any topical or oral corticosteroids or TCIs between 2005 and 2018 (start and end of data collection). The risk of inclusion of AD-patients in the reference cohort is therefore low. The reference cohort was matched to the AD cohort with replacement on birth-year, sex and region. After matching, three reference cohorts, corresponding to the analyzed age cohorts (paediatric, adolescent and adult) were created.

Direct and indirect healthcare resource costs

Healthcare cost for AD patients and controls was calculated in each year after the index as the sum of the cost of all secondary and primary care contacts and all filled prescriptions, independent of the principal diagnosis or ATC-code which allowed us to understand the costs associated with AD itself and also with potential comorbidities. The cost of healthcare visits with an AD-diagnosis (L20+) as the principal diagnosis (AD-related) was calculated separately from all other healthcare visits in the AD-cohorts. Likewise, the cost of filled prescriptions of AD-treatments was calculated separately from the cost of other non-AD-treatments, which also allowed us to potentially understand the role of comorbidities on the costs associated to AD. Direct costs associated with secondary care contacts were calculated using disease-related group (DRG) codes registered for all healthcare contacts linked with corresponding year-specific DRG cost weights. Costs of primary care visits (€158.56 per visit) were estimated based on public unit costs.[28] The cost for primary care visits obtained from 1/3 of the population was extrapolated to a national level by multiplying the average cost (by age and severity groups) by the estimated number of AD patients in these groups in the total population. Costs for filled prescriptions were based on the pharmacy retail price and collected from the PDR.

The indirect cost paid to parents for taking care of their sick children with AD aged 0–12 years (maximum age as per the system and set by the Swedish government) was extracted directly from the SIR and corresponds to the total amount of government compensation paid for childcare during follow-up. No indirect costs in the adolescent age cohort were estimated since parents to

adolescents are not eligible for compensation and adolescents have not entered the by law stipulated age for labour market participation and are thus ineligible for compensation due to long-term sick leave. The indirect costs for long-term sick leave days consumed by adults with AD were collected from the SIR and corresponds to the total amount of sick leave compensation paid by the government to the individual during follow-up. All sick leave, independent of reason, was included. All costs were inflated using the Swedish inflation rate (Consumer Price Index) from the reported year to 2020 SEK, and then converted to EUR using the 2020 SEK/EUR exchange rate of 10.49.[29]

Statistical analyses

Descriptive statistics of patient characteristics were computed for paediatric, adolescent and adult patients with AD compared to that of each respective reference cohort as mean ± standard deviation (SD) for continuous variables and number and percentage for categorical variables. Cost outcomes were presented stratified by age group and severity level. Comparisons between the AD cohorts and non-AD reference cohorts were tested using a significance level of 0.05 to indicate statistically significant differences.

A generalized linear model with a gamma distribution and a log-link function was used to evaluate the possible association between healthcare costs and indirect costs 1 year after index date and the presence of AD (by disease severity: M2M and severe AD), respectively.[30,31] Separate models were estimated for each age group. In addition, two separate models were used to estimate healthcare costs, one including costs of secondary care and dispensed medication and a second model which also included the cost of primary care. Moreover, in the paediatric and adult age cohorts, indirect costs (for care of sick children and long-term sick leave, respectively) were estimated in separate models. All models were adjusted for severity, sex, comorbidity profile, region of residence and index year. All data management and statistical analyses were performed in STATA 16.[32]

RESULTS

A total of 195,719 paediatric AD patients (85% M2M, 15% severe), 34,717 adolescent AD patients (85% M2M, 15% severe), 107,774 adult AD patients (86% M2M and 14% severe) and an equal number (to each age-group) of matched controls were included in this study. Patient characteristics are presented in Table 2.

Direct healthcare costs

Compared with matched controls, the annual mean per patient direct healthcare cost (including secondary care visits, primary care visits and dispensed prescriptions) in AD patients (related or unrelated to the AD diagnosis), was €941 (€2084 vs. €1142) and €1259 (€2401 vs. €1142) higher in the first year after index ($p < 0.05$) in M2M and severe AD paediatric patients, respectively. In adolescent patients with M2M and severe AD, the mean per patient direct healthcare cost was €816 (€1558 vs. €742) and €1260 (€2003 vs. €742) higher in the first year after the index date ($p < 0.05$), respectively, compared with matched controls. In the analyses comprising adults, the mean per patient direct healthcare cost was €1583 (€2991 vs. €1408) and €2963 (€4371 vs. €1408) higher in M2M and severe AD adults, respectively, compared to that of controls in the first year after the index date ($p < 0.05$). The difference in mean direct healthcare cost between the M2M and severe AD cohorts and the matched control cohorts declined over time during follow-up but the mean direct cost was consistently statistically significantly higher in AD patients in all three age groups compared to controls (Figure 1). Detailed results including underlying healthcare resource use can be found in Supporting Information: Tables S4–S9.

Figure 2 shows the direct cost composition by age and severity in the first year after the index date. AD-related specific healthcare resource use contributed to between 8.5% and 17.0% of the difference in the annual mean healthcare costs between AD cohorts and the matched controls. The incremental cost of the AD-cohort compared to the non-AD reference cohort was mainly driven by primary- and specialist healthcare visits due to comorbid medical conditions (potential AD comorbidities) which was higher in both M2M and severe AD. In the generalized linear model for healthcare costs, which included costs of healthcare visits to primary- and secondary care and dispensed prescriptions, the cost of patients with AD was significantly higher compared to that of non-AD reference cohorts after adjusting for comorbid medical conditions at baseline (see Table 3). The models also showed that healthcare costs increased with severity in all age cohorts.

Indirect costs

Comparing parents of children with AD to parents of matched controls, the annual mean (per patient) indirect cost of childcare was €69 and €78 higher in the first year after the index ($p < 0.05$) in parents to paediatric patients with M2M and severe AD, respectively. The mean difference in indirect costs for parents of paediatric

TABLE 2 Summary of patient characteristics

	Paediatric (age < 12 years)			Adolescent (age ≥ 12 to < 18)			Adult (age ≥ 18 years)		
	Mild-to-moderate AD (*N* = 165,564)	Severe AD (*N* = 30,155)	Non-AD reference cohort (*N* = 195,719)	Mild-to-moderate AD (*N* = 29,466)	Severe AD (*N* = 5251)	Non-AD reference cohort (*N* = 34,717)	Mild-to-moderate AD (*n* = 92,413)	Severe AD (*n* = 15,361)	Non-AD reference cohort (*n* = 107,774)
	Mean (SD)								
Age at index, years (SD)	3.06 (3.04)	4.66 (3.70)	3.31 (3.22)	15.07 (1.71)	15.36 (1.65)	15.12 (1.70)	42.21 (18.76)	46.78 (18.46)	42.86 (18.79)
Annual mean household income[a], €1000 (SD)	40.65 (70.75)	47.00 (51.98)	47.54 (58.47)	49.40 (67.11)	51.35 (105.24)	49.71 (44.27)	41.02 (70.67)	40.47 (44.75)	38.71 (63.33)
Annual mean number of specialist visits[b], (SD)	1.35 (2.50)	1.45 (3.84)	0.72 (1.59)	1.07 (2.40)	1.09 (2.92)	0.59 (1.54)	1.79 (3.66)	2.85 (4.81)	0.84 (2.14)
Annual mean days of hospitalization[b], (SD)	0.60 (5.25)	1.12 (10.46)	0.33 (3.56)	0.28 (4.39)	0.43 (6.11)	0.15 (3.25)	0.84 (7.55)	1.01 (5.72)	0.57 (8.22)
Medications[b], number of unique dispensations (SD)	4.91 (50.70)	8.51 (128.37)	2.04 (35.80)	5.39 (32.08)	5.83 (62.05)	2.65 (39.68)	14.97 (51.13)	24.74 (49.73)	6.53 (34.14)
	N (%)								
Gender, *n* (%)									
Male	88,320 (53.3)	15,869 (52.6)	104,135 (53.2)	11,770 (39.9)	2352 (44.8)	14,177 (40.8)	60,050 (65.0)	9577 (62.4)	69,627 (64.6)
Female	77,244 (46.7)	14,286 (47.4)	91,584 (46.8)	17,696 (60.1)	2899 (55.2)	20,540 (59.2)	32,363 (35)	5784 (37.7)	38,147 (35.4)
AD identification[d], *n* (%)									
Primary care diagnosis	25,022 (15.0)	2591 (8.5)	NA	4538 (15.4)	428 (8.1)	NA	41,804 (45.2)	2871 (18.7)	NA
Secondary care diagnosis	56,676 (34.0)	9617 (31.6)	NA	5746 (19.5)	593 (11.3)	NA	50,609 (54.8)	12,490 (81.3)	NA
Dispensation of TCIs	2064 (1.2)	208 (0.7)	NA	1945 (6.6)	84 (1.6)	NA	NA	NA	NA

(Continues)

TABLE 2 (Continued)

	Paediatric (age < 12 years)			Adolescent (age ≥ 12 to < 18)			Adult (age ≥ 18 years)		
	Mild-to-moderate AD (*N* = 165,564)	**Severe AD (*N* = 30,155)**	**Non-AD reference cohort (*N* = 195,719)**	**Mild-to-moderate AD (*N* = 29,466)**	**Severe AD (*N* = 5251)**	**Non-AD reference cohort (*N* = 34,717)**	**Mild-to-moderate AD (*n* = 92,413)**	**Severe AD (*n* = 15,361)**	**Non-AD reference cohort (*n* = 107,774)**
Dispensation of TCSs	91,731 (55.0)	21,194 (69.5)	NA	18,298 (62.1)	4411 (84.0)	NA	NA	NA	NA
Comorbid diseases[c], *n* (%)									
Asthma	19,154 (11.6)	2829 (9.4)	7050 (3.6)	2671 (9.1)	336 (6.4)	954 (2.7)	6937 (7.5)	1170 (7.6)	860 (0.8)
Allergic rhinitis	3896 (2.4)	745 (2.5)	773 (0.4)	2355 (8.0)	255 (4.9)	708 (2.0)	7560 (8.2)	1078 (7.0)	1262 (1.2)
Conjunctivitis	3830 (2.3)	760 (2.5)	2084 (1.1)	1003 (3.4)	145 (2.8)	398 (1.1)	4731 (5.1)	799 (5.2)	1499 (1.4)
Skin diseases excl. AD	5681 (3.4)	1135 (3.8)	868 (0.4)	605 (2.1)	120 (2.3)	135 (0.4)	15,768 (17.1)	5661 (36.9)	624 (0.6)
Food hypersensitivity incl. IgE sensitization	12,007 (7.3)	1612 (5.3)	2677 (1.4)	928 (3.1)	109 (2.1)	193 (0.6)	2342 (2.5)	455 (3.0)	393 (0.4)
Drug hypersensitivity	416 (0.3)	115 (0.4)	227 (0.1)	97 (0.3)	26 (0.5)	28 (0.1)	901 (1.0)	206 (1.3)	243 (0.2)
Venom hypersensitivity	266 (0.2)	72 (0.2)	220 (0.1)	60 (0.2)	10 (0.2)	44 (0.1)	183 (0.2)	33 (0.2)	65 (0.1)
Anaphylaxis	586 (0.4)	85 (0.3)	59 (0.0)	129 (0.4)	18 (0.3)	9 (0.0)	618 (0.7)	74 (0.5)	24 (0.0)
Neurological and psychiatric disorders	3500 (2.1)	1067 (3.5)	2634 (1.3)	3176 (10.8)	717 (13.7)	2905 (8.4)	18,544 (20.1)	3231 (21.0)	14,785 (13.7)
Infections	54,932 (33.2)	9996 (33.1)	42,361 (21.6)	3912 (13.3)	708 (13.5)	2964 (8.5)	11,775 (12.7)	2425 (15.8)	6342 (5.9)
Immunological and inflammatory disorders	1152 (0.7)	393 (1.3)	727 (0.4)	824 (2.8)	186 (3.5)	499 (1.4)	10,111 (10.9)	3091 (20.1)	5897 (5.5)
Type 1 diabetes (T1D)	283 (0.2)	96 (0.3)	137 (0.1)	185 (0.6)	37 (0.7)	188 (0.5)	942 (1.0)	202 (1.3)	950 (0.9)

TABLE 2 (Continued)

	Paediatric (age < 12 years)			Adolescent (age ≥ 12 to < 18)			Adult (age ≥ 18 years)		
	Mild-to-moderate AD (*N* = 165,564)	Severe AD (*N* = 30,155)	Non-AD reference cohort (*N* = 195,719)	Mild-to-moderate AD (*N* = 29,466)	Severe AD (*N* = 5251)	Non-AD reference cohort (*N* = 34,717)	Mild-to-moderate AD (*n* = 92,413)	Severe AD (*n* = 15,361)	Non-AD reference cohort (*n* = 107,774)
Type 2 diabetes (T2D)	8 (0.0)	2 (0.0)	5 (0.0)	13 (0.0)	2 (0.0)	5 (0.0)	2094 (2.3)	511 (3.3)	1636 (1.5)
Endocrine and metabolic disorders (excl. T1D and T2D)	2864 (1.7)	723 (2.4)	1931 (1.0)	800 (2.7)	157 (3.0)	598 (1.7)	5200 (5.6)	1130 (7.4)	3755 (3.5)
Cardiovascular	221 (0.1)	80 (0.3)	113 (0.1)	59 (0.2)	15 (0.3)	32 (0.1)	9412 (10.2)	2187 (14.2)	7912 (7.3)
Skeletal disorders	4266 (2.6)	1233 (4.1)	5363 (2.7)	3964 (13.5)	751 (14.3)	4348 (12.5)	9250 (10.0)	1590 (10.3)	9312 (8.6)
Malignancies	189 (0.1)	97 (0.3)	92 (0.0)	75 (0.3)	18 (0.3)	40 (0.1)	4438 (4.8)	943 (6.1)	3,319 (3.1)
Ocular disorders	400 (0.2)	129 (0.4)	363 (0.2)	246 (0.8)	52 (1)	185 (0.5)	6449 (7.0)	1318 (8.6)	4230 (3.9)

Abbreviations: AD, atopic dermatitis; M2M, mild-to-moderate; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; SD, standard deviation.

[a]Measured during the calendar year before index date.

[b]Measured during the year before index date.

[c]Measured from 01 July 2005 to—and including—index date.

[d]This may sum to more than 100%, as patients can fulfill one or both of inclusion criteria 1 and 2. See Supporting Information for ICD-10 codes used to define comorbidities (Supporting Information: Table S3).

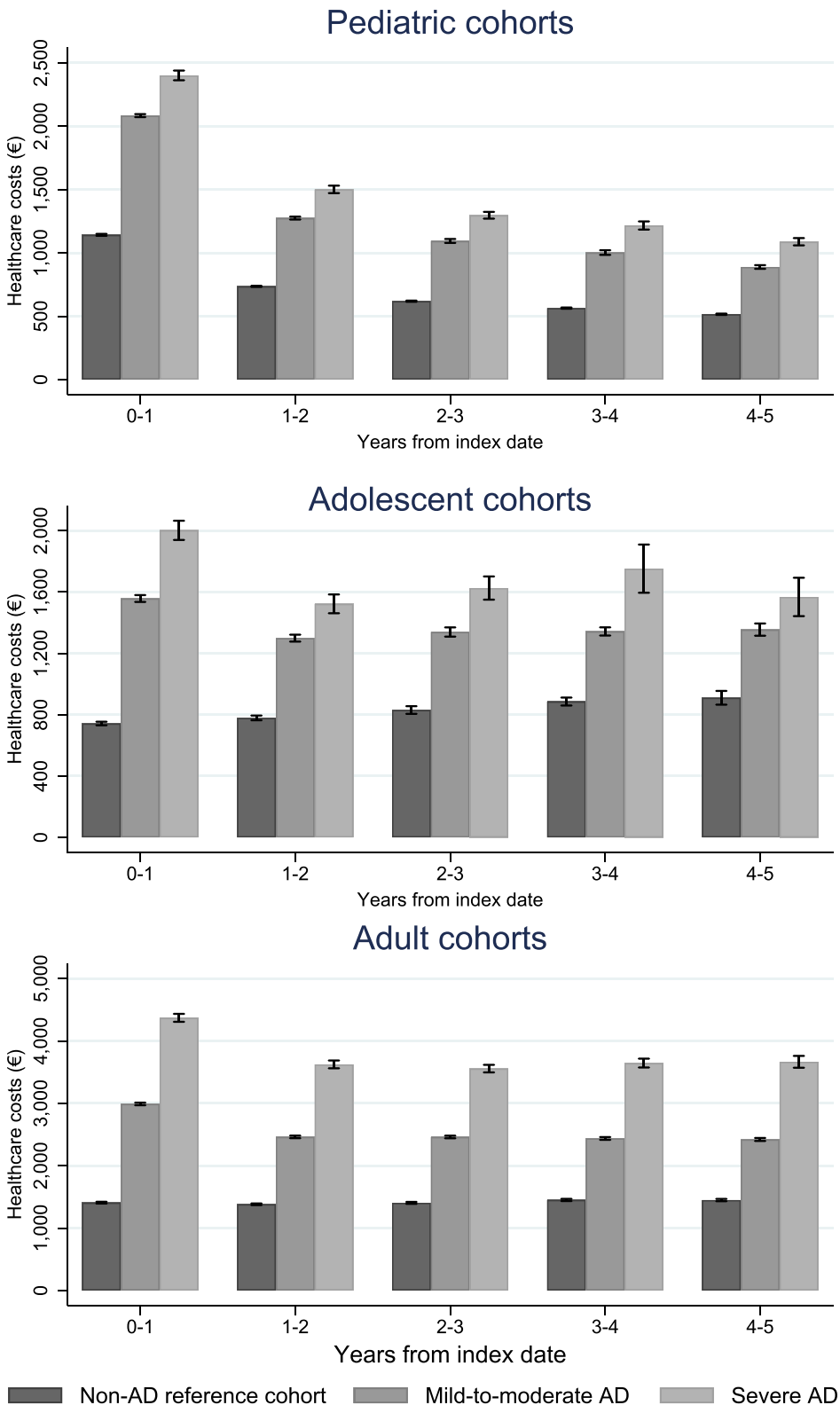

FIGURE 1 Annual mean (per patient) direct healthcare costs including the cost of primary and secondary care visits and dispensed prescriptions by year after index date, age cohort and severity, in EUR 2020. The error bars represent 95% confidence interval.

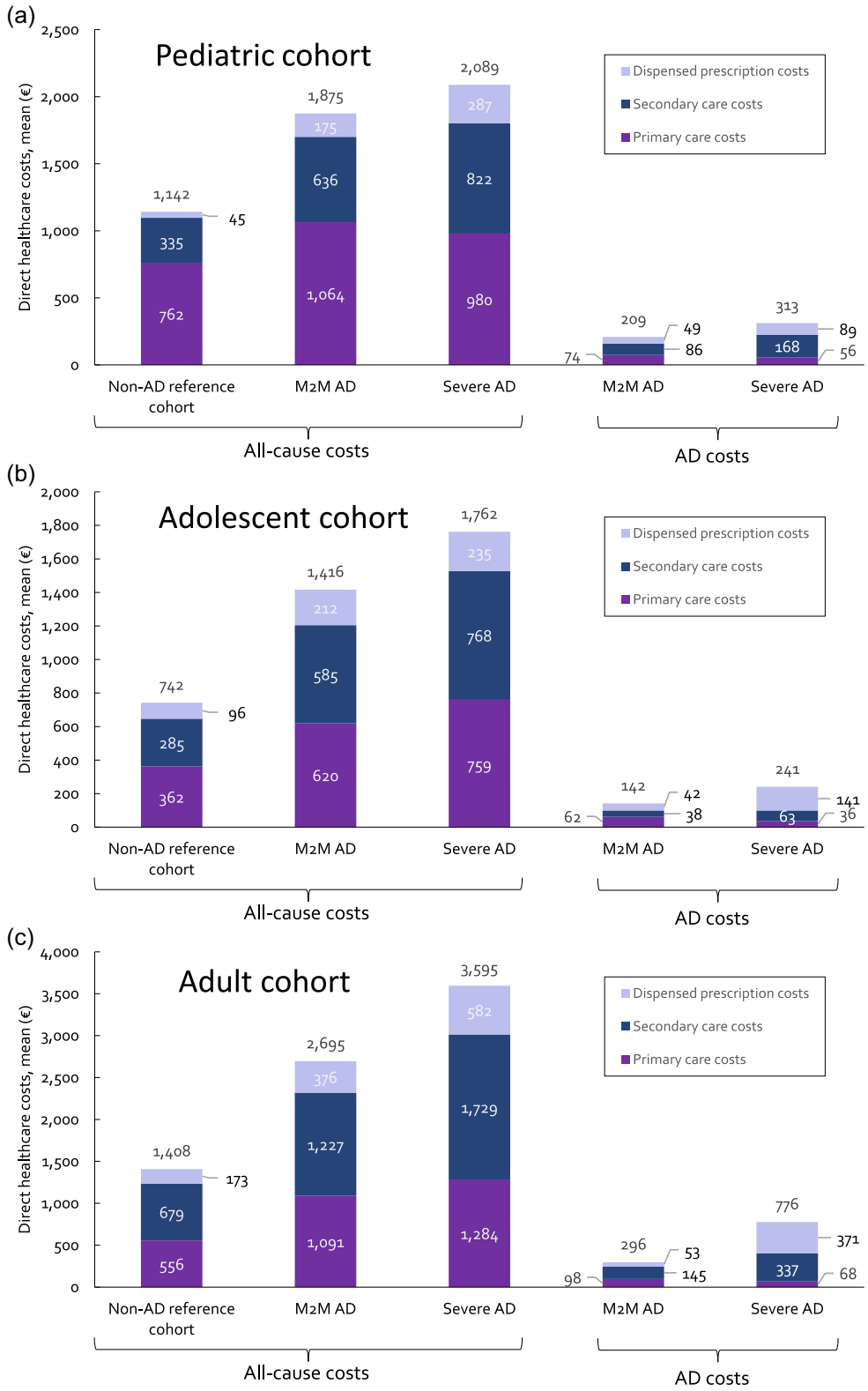

FIGURE 2 Annual mean (per patient) direct healthcare costs (EUR 2020) by type in the first year after index date in (a) paediatric age cohort, (b) adolescent age cohort and (c) adult age cohort. AD-treatment includes cost of topical corticosteroids, topical calcineurin inhibitors, emollients, dupilumab, systemic steroids prescribed by a dermatologist and systemic immunosuppressants. AD-related primary and secondary visits include the cost of healthcare visits for which atopic dermatitis (L20+) was the principal diagnosis. All-cause costs include the cost of all other healthcare visits and dispensations in patients identified with AD. The sum of three types of cost may not exactly equate to the total average cost because of rounding error. AD, atopic dermatitis.

TABLE 3 Generalized linear model of determinants of 1-year healthcare cost and 1-year indirect costs in patients with AD compared to the non-AD reference cohort by age-group

	Paediatric age-group			Adolescent age-group		Adult age-group		
	Healthcare costs[a] (excl. primary care visits)	Total direct healthcare costs[b]	Cost of childcare	Healthcare costs[a] (excl. primary care visits)	Total direct healthcare costs[b]	Healthcare costs[a] (excl. primary care visits)	Total direct healthcare costs[b]	Cost of long-term sick leave
Presence of AD								
M2M AD versus non-AD	1.91* (1.82–2.00)	1.55* (1.52–1.59)	1.07* (1.05–1.08)	2.05* (1.89–2.22)	1.93* (1.79–2.08)	1.76* (1.70–1.82)	1.73* (1.68–1.78)	1.55* (1.47–1.65)
Severe AD versus non-AD	2.51* (2.37–2.65)	1.65* (1.56–1.74)	1.07* (1.04–1.10)	2.75* (2.47–3.05)	2.33* (2.12–2.56)	2.56* (2.45–2.68)	2.10* (2.00–2.20)	2.05* (1.87–2.26)
Male versus female	1.35* (1.30–1.41)	1.23* (1.20–1.26)	0.99* (0.98–1.00)	0.92* (0.86–0.99)	0.71* (0.67–0.76)	0.91* (0.87–0.94)	0.83* (0.81–0.86)	0.71* (0.66–0.75)
Presence of comorbidities								
Asthma	1.22* (1.16–1.28)	1.04 (0.98–1.10)	1.33* (1.30–1.36)	1.20* (1.10–1.31)	1.22* (1.09–1.36)	1.45* (1.37–1.53)	1.25* (1.17–1.34)	1.13* (1.00–1.26)
Allergic rhinitis	0.83* (0.77–0.89)	0.67* (0.62–0.73)	0.89* (0.85–0.93)	1.33* (1.18–1.50)	1.27* (1.10–1.46)	0.97 (0.92–1.02)	0.99 (0.94–1.04)	1.05 (0.94–1.18)
Conjunctivitis	1.02 (0.95–1.10)	1.02 (0.96–1.08)	1.08* (1.04–1.13)	0.98 (0.86–1.12)	1.02 (0.89–1.16)	1.02 (0.96–1.08)	0.99 (0.93–1.05)	1.27* (1.10–1.47)
Skin diseases excl. AD	1.48* (1.43–1.53)	1.30* (1.27–1.34)	0.92* (0.90–0.94)	1.30* (1.19–1.42)	0.99 (0.90–1.10)	1.16* (1.12–1.20)	1.09* (1.05–1.13)	1.17* (1.09–1.26)
Food hyper-sensitivity incl. IgE sensitization	1.34* (1.28–1.42)	1.22* (1.15–1.28)	1.08* (1.05–1.11)	0.94 (0.82–1.07)	0.93 (0.80–1.08)	0.95 (0.87–1.04)	0.96 (0.88–1.06)	1.12 (0.92–1.38)
Drug hyper-sensitivity	2.36* (1.49–3.72)	1.94* (1.20–3.13)	1.16* (1.04–1.28)	1.95* (1.22–3.14)	1.62 (0.93–2.83)	1.38* (1.17–1.63)	1.40* (1.19–1.64)	1.65* (1.29–2.12)
Venom hyper-sensitivity	0.74* (0.59–0.92)	0.73* (0.57–0.93)	1.19* (1.05–1.36)	0.99 (0.57–1.73)	0.9 (0.62–1.30)	1.25 (0.85–1.82)	1.09 (0.86–1.39)	1.02 (0.59–1.74)
Anaphylaxis	0.94 (0.76–1.16)	0.74* (0.64–0.86)	0.95 (0.85–1.05)	1.08 (0.79–1.49)	0.99 (0.72–1.37)	1.02 (0.88–1.18)	0.97 (0.84–1.11)	1.03 (0.74–1.45)
Neurological and psychiatric disorders	2.42* (2.26–2.60)	1.46* (1.33–1.59)	1.14* (1.09–1.21)	3.24* (3.00–3.50)	2.15* (1.98–2.34)	2.44* (2.32–2.56)	1.95* (1.87–2.04)	2.81* (2.67–2.97)
Infections	1.29* (1.25–1.34)	1.06* (1.03–1.08)	1.33* (1.32–1.35)	1.68* (1.47–1.91)	1.23* (1.14–1.32)	1.40* (1.33–1.47)	1.32* (1.26–1.38)	1.10* (1.01–1.19)
Immunological and inflammatory disorders	1.41* (1.14–1.74)	1.1 (0.85–1.42)	1.06 (0.96–1.17)	2.38* (1.95–2.90)	1.69* (1.36–2.10)	1.79* (1.72–1.87)	1.62* (1.56–1.68)	1.47* (1.36–1.59)

TABLE 3 (Continued)

	Paediatric age-group			Adolescent age-group		Adult age-group		
	Healthcare costs[a] (excl. primary care visits)	Total direct healthcare costs[b]	Cost of childcare	Healthcare costs[a] (excl. primary care visits)	Total direct healthcare costs[b]	Healthcare costs[a] (excl. primary care visits)	Total direct healthcare costs[b]	Cost of long-term sick leave
Type 1 diabetes	7.21*	3.45*	1.47*	8.16*	4.96*	2.09*	1.56*	1.28
	(6.55–7.94)	(3.00–3.97)	(1.21–1.77)	(7.37–9.03)	(4.30–5.71)	(1.90–2.29)	(1.40–1.74)	(0.97–1.69)
Type 2 diabetes	N/a	N/a	N/a	N/a	N/a	1.50*	1.54*	0.70*
						(1.35–1.67)	(1.40–1.70)	(0.55–0.88)
Endocrine and metabolic disorders (excluding T1D and T2D)	2.38*	1.19*	1.15*	1.73*	1.44*	1.32*	1.21*	1.38*
	(2.05–2.76)	(1.01–1.40)	(1.09–1.22)	(1.41–2.14)	(1.12–1.85)	(1.23–1.42)	(1.13–1.30)	(1.22–1.56)
Skeletal disorders	0.78*	0.65*	0.99	1.20*	1.20*	1.17*	1.18*	1.15*
	(0.70–0.87)	(0.61–0.70)	(0.95–1.02)	(1.07–1.35)	(1.10–1.31)	(1.12–1.23)	(1.13–1.23)	(1.06–1.26)
Malignancies	20.51*	13.30*	7.68*	11.60*	10.73*	2.05*	1.64*	1.04
	(15.83–26.58)	(8.51–20.78)	(6.44–9.17)	(6.90–19.53)	(5.00–23.02)	(1.90–2.21)	(1.55–1.73)	(0.91–1.20)
Ocular manifestations	1.38*	1.11	0.99	1.79*	1.21	1.27*	1.25*	0.84*
	(1.13–1.69)	(0.88–1.41)	(0.87–1.13)	(1.26–2.55)	(0.96–1.53)	(1.21–1.34)	(1.20–1.31)	(0.73–0.96)
Cardiovascular	N/a	N/a	N/a	N/a	N/a	2.18*	1.91*	0.83*
						(2.08–2.29)	(1.83–2.00)	(0.74–0.92)

Note: The coefficients in each cell represent the cost-ratio for each variable. The numbers in parenthesis are the 95% confidence intervals. Adjustment calendar year of index, and region of residence not reported. Indirect costs were not estimated in the adolescent age cohort.

Abbreviations: AD, atopic dermatitis; IgE, immunoglobulin E; M2M, mild-to-moderate; T1D, type 1 diabetes; T2D, type 2 diabetes.

[a]Cost of secondary care visits and dispensed medications for the whole study population.

[b]Cost of primary- and secondary care visits and dispensed medication for the part of study population covered by the primary care databases. The estimated cost-ratios should be interpreted as the percentage increase or decrease in costs with respect to the reference value. For example, the coefficient for mild-to-moderate AD (1.91) in the first model implies that the presence of mild-to-moderate AD is associated with an increase by 91% in direct healthcare costs compared with the reference cohort.

*$p < 0.05$.

patients with M2M AD was higher in the second year compared to the first year (€96 vs. €69, $p < 0.05$) while it decreased for parents of paediatric patients with severe AD. After the second year, the mean difference in cost of childcare for both paediatric M2M and severe AD compared to matched controls continued to be statistically significantly different during follow-up (see Figure 3).

Indirect costs for long-term sick leave in adult AD patients increased over time after the index date. Compared with matched controls, the annual mean (per patient) indirect cost of adult AD patients with M2M and severe AD was €148 and €263 higher, respectively, in the first year following the index date ($p < 0.05$). In the fifth year of follow-up, the corresponding costs were €200 and €271 higher in the M2M and severe adult AD cohort, respectively, compared to matched controls ($p < 0.05$). All differences were statistically significant (see Figure 3).

Societal economic burden of AD

Compared to the reference cohort in each respective age cohort, the total healthcare cost for secondary care visits, primary care visits (extrapolated to a national level) and dispensed prescriptions one year after the index was €156 and €38 million higher in M2M and severe paediatric patients, €24 and €7 million higher in M2M and severe adolescent patients, and €146 and €46 million higher in

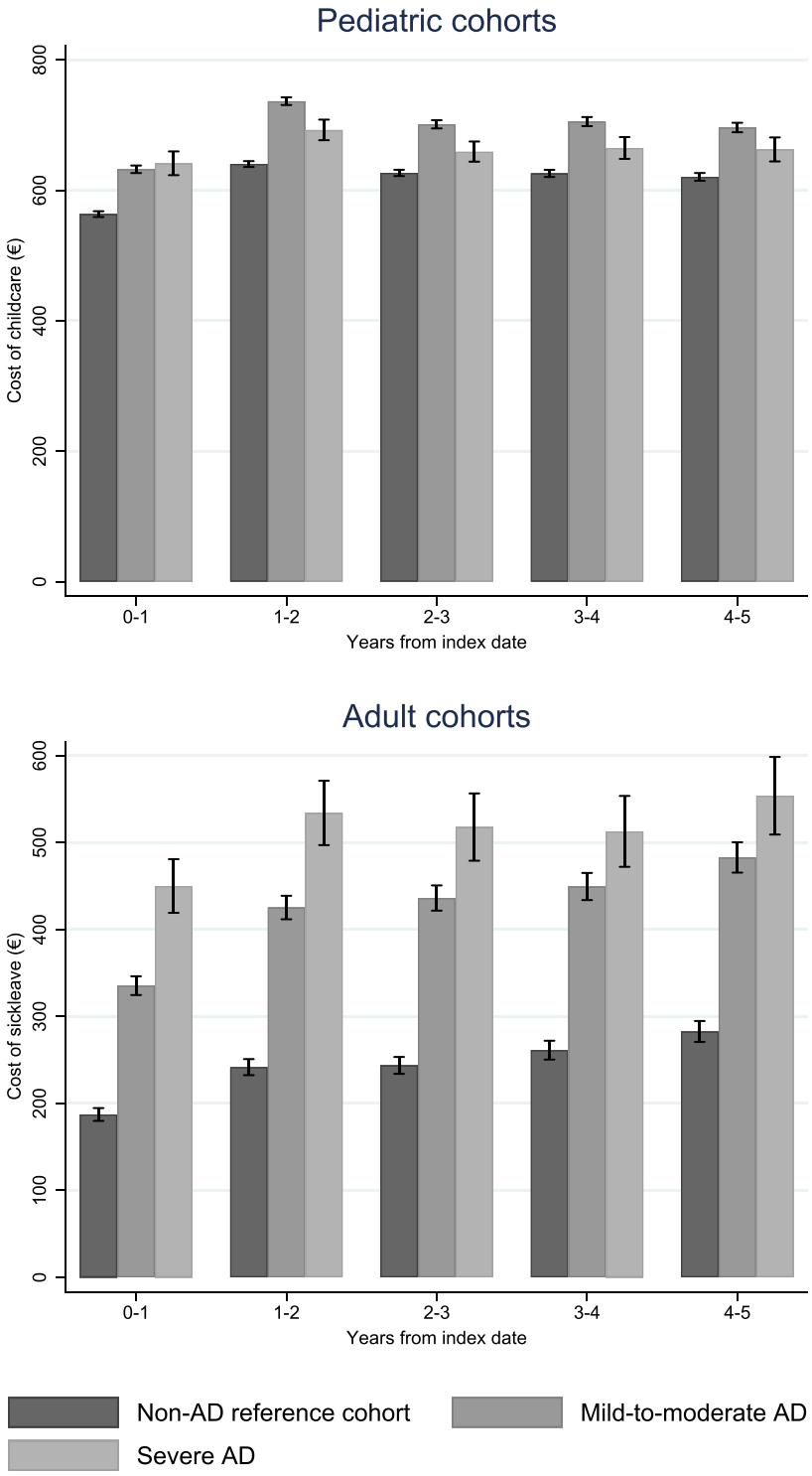

FIGURE 3 Annual mean (per patient) indirect costs over time. In the paediatric cohorts, indirect costs represent the compensation paid by the government to parents for taking care of sick children (aged 12 or less). In the adult cohort, indirect costs represent the compensation paid by the government to the individual for sick leave periods longer than 14 days. The error bars represent 95% confidence interval.

M2M and severe adult patients. The incremental total healthcare care cost for healthcare visits due specifically to AD and AD-treatment was €44, €5 and €39 million in the paediatric, adolescent and adult age group, respectively. Total indirect costs were €11 and €2 million higher in M2M and severe paediatric patients, respectively, in the first year after the index date. In adult patients with AD, total indirect costs were €14 and €4 million higher in M2M and severe AD, respectively, compared to the non-AD reference cohort. On a population level, the total incremental societal economic burden (sum of direct and indirect costs) of AD was €448 million in the first year after the index date. Of the total incremental societal burden in the first year after the index date, patients with M2M AD accounted for 78% (€351 million) and patients with severe AD for 22% (€96 million). Direct healthcare

costs represented 93% (€416 million) and indirect costs represented 7% (€31 million).

Sensitivity analysis

A sensitivity analysis using only diagnosis codes of AD (i.e., filled prescriptions not used to merit inclusion) to identify the paediatric and adolescent AD-cohorts showed similar results as in the base case analysis. Compared with matched controls, the annual mean (per patient) direct healthcare cost, including the cost for secondary care visits, primary care visits and dispensed prescriptions, was €984 (€2039 vs. €1055) and €1205 (€2260 vs. €1055) higher in the first year after index ($p < 0.05$) in M2M and severe AD paediatric patients, respectively, compared to matched controls. In adolescent patients with M2M and severe AD, the mean healthcare cost was €890 (€1687 vs. €798) and €1142 (€1940 vs. €798) higher in the first year after the index date ($p < 0.05$), respectively, compared with matched controls.

DISCUSSION

In this large, matched cohort study, we show that AD, a common, chronic and relapsing inflammatory skin disease is associated with a significant societal economic burden in Sweden. The burden of AD is mainly driven by increased direct healthcare costs, but indirect costs including parental leave to care for a sick child with AD and long-term sick leave in the adult AD population were also significantly higher than matched controls. In all age groups, patients with severe AD had a higher economic burden per patient, but due to the high prevalence of M2M AD the economic burden of AD at a population level was higher for patients with M2M AD. Despite being often considered a childhood disease, the economic burden of AD was also shown to be significant in adulthood.

The proportion of healthcare costs directly associated with AD-related healthcare visits and dispensed medications varied across the three age groups, but incremental healthcare costs in the AD-cohort were largely comprised of healthcare visits and medical dispensations not directly used to manage AD symptoms. The AD-cohort also had a higher prevalence of comorbidities at baseline. The link between AD and other disease is well established, in particular for atopic comorbidities but this difference may also be related to the cohort selection. In this study, the AD cohort was required to have a healthcare visit or a dispensation to be included in the cohort whereas no such criteria was imposed on the non-AD reference cohort. However, healthcare costs remained statistically significantly higher in patients with AD after accounting for the prevalence of comorbidities at baseline which was higher in the AD-cohort compared to the non-AD reference cohort. The higher use of non-AD healthcare resources reported in this study was consistent with that reported in previous studies[33] which also found that healthcare resource use directly associated with AD was significant, but not the main driver of total healthcare costs. There may be several explanations for this. Atopic dermatitis is often the first clinical manifestation of atopic diseases but the role of AD in other non-atopic diseases including anxiety, depression, diabetes, cardiovascular disorders and infections among others is well-documented.[34–38] Two recent comprehensive observational matched cohort studies found that AD was associated with an increased risk of developing several comorbidities. The management of these diseases may not only be more costly than the management of AD but may also be considered more urgent to care for than the AD itself. In turn, this may explain the low level of costs directly associated to AD.

Cost of illness studies in AD are rare and most studies have focused on the cost in patients with severe AD. Ortsäter et al.[18] estimated healthcare costs, including costs of secondary care visits and dispensed prescriptions, in a paediatric population (aged 0–14) with M2M AD versus a reference cohort. The incremental mean (per patient) healthcare cost was €587, which is similar to the results in the present study. Thyssen et al.[39] estimated the direct healthcare costs and indirect costs in 5245 adult patients with moderate-to-severe AD in Denmark. During the first year after the index, healthcare costs per patient were €4930 higher compared to the reference cohort. This estimate was more than double the estimate in the present study and was likely driven by higher AD-related healthcare contacts and medication dispensations. A Finnish study found that incremental costs (both direct and indirect) in infants diagnosed with AD was €295 higher compared with infants without AD and that parents paid for 43% of the costs arising from AD.[40] The proportion of indirect costs compared with the total societal economic burden observed in our study was low. We also found that while severe AD (compared with M2M AD) is an important differentiator of healthcare costs and the cost of long-term sick leave, this was not the case for the cost of childcare. While this and other studies found that indirect costs do not drive the total economic burden of AD, Thyssen et al. showed that gross earnings in patients with AD is significantly lower than that of the general population indicating that lower incomes in AD patients can be an important source of societal opportunity costs.

The SIR database which was used to estimate the cost of long-term sick leave in our study only included periods of sick leave that lasted longer than 14 days. The results showed that the adult AD-cohort had more periods of long-term sick leave compared to the matched control cohort. While these were probably not a direct consequence of AD-symptoms, the higher frequency of long-term sick leave might also indicate that patients with AD have more short-term sick leave periods (i.e., lasting less than 14 days) which were then not accounted for in this study. Therefore, the estimated indirect cost of sick leave in the AD-population is probably a conservative estimate. Moreover, both components of indirect cost (childcare and long-term sick leave) were estimated as transfer costs rather than opportunity costs and are therefore a conservative estimate of the actual cost to society.

Strengths

The present study has many strengths. First, it utilized population-based data with complete register coverage and long follow-up including primary care data from two of the three largest regions in Sweden. Second, this study combined both primary and secondary care registers as a data source for the identification of patients with AD, which increases the heterogeneity of the study population in terms of the severity of the disease. Third, this study adjusted for a wide range of comorbidities as well as sociodemographic characteristics in estimating drivers of cost. This allows for a comprehensive and likely unbiased evaluation of the association between the presence of AD diagnosis, and direct and indirect costs in comparison to a matched control population in selected age groups and by disease severity in a real-world setting. Moreover, this study is the first of its kind to estimate the indirect cost associated with parental care for sick children with AD. Together, these strengths enhance the external validity of the study and provide for a robust assessment of the societal economic burden of AD.

Limitations

We also acknowledge that this study has some limitations. An objective clinical measure of disease severity, such as Eczema Area and Severity Index (EASI) or Severity Scoring of Atopic Dermatitis (SCORAD) was not available in the databases used in this study. Rather, severity stratification relied on the type of healthcare contacts and treatments used as a proxy measure for disease severity. It cannot, therefore, be excluded that some M2M patients may have been classified as severe AD patients after having used a potent TCS to control a flare. However, this limitation would not have an impact on the total burden of AD (i.e., combining the cost of M2M and severe AD) estimated in this study. Yet, the proportion of severe AD (~15%) is in close proximity to the proportion of severe AD observed in other studies.[41,42] Moreover, access to primary care data was only partial in this study. Hence, some patients were identified through diagnosis while others were only identified through a prescription algorithm. This may have contributed to some inaccuracies in patient selection for some patients in the M2M group and should be studied further. Finally, treatments purchased over-the-counter (emollients and mild TCSs) are not included in the PDR and the cost of these was hence not accounted for in this study. Moreover, this study did not account for any other out-of-pocket costs incurred in relation to healthcare visits or treatments, likely underestimating the total societal burden of AD. Likewise, the impact of AD on earnings was not accounted for in this study which implies that the size of indirect cost in the present study is probably underestimated.

CONCLUSIONS

Atopic dermatitis is associated with a significant societal economic burden. Healthcare costs per patient were higher in patients with severe AD compared with patients with M2M AD. However, the total incremental societal economic burden on a population level was driven primarily by healthcare costs in patients with M2M AD, given its higher prevalence. Another important driver of costs was healthcare care resource utilization (visits and medications) not directly used to manage AD symptoms, that might be related to the treatment of AD comorbidities. These constitute a large proportion of the total incremental costs of healthcare for AD patients, highlighting the need to optimize the provision of care and treatment of AD with attention also to comorbidities. This may assist in the improvement of AD patient outcomes and in reducing the direct and indirect costs of patient care.

AUTHOR CONTRIBUTIONS

All authors participated in the conceptualization and design of this study. Ingrid Lindberg, Gustaf Ortsäter, Alexander Rieem Dun and Kirk Geale were involved in data curation, formal analysis, investigation, provision of resources, software programming and creation of visualizations. Anna De Geer, Dan Henrohn, Petra Neregård, Amy Cha, Joseph C. Cappelleri, William Romero and Maureen P. Neary were involved in supervision and

validation of the work. Maureen P. Neary acquired financial support for the study leading to this publication. Jacob Pontoppidan Thyssen, Laura B. von Kobyletzki and Alexandra Metsini provided clinical expertise. Ingrid Lindberg, Gustaf Ortsäter, Alexander Rieem Dun and Kirk Geale drafted the manuscript. All authors reviewed and approved the final manuscript. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have provided final approval of the version to be published.

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CONFLICTS OF INTEREST

A. C. and J. C. C. are employed by Pfizer Inc. and own Pfizer stock and/or stock options. M. P. N. was an amployee of Pfizer Inc and owned Pfizer stock and/or stock options at the time of analysis and manuscript submission. W. R. is employed by Pfizer Ltd. and owns Pfizer stock and/or stock options. D. H. is employed by Pfizer AB and owns Pfizer stocks. P. N. was an employee of Pfizer AB and owned Pfizer stocks at the time of this study and is at the time of manuscript submission, an employee of UCB Pharma AB. A. D. G. was an employee of Pfizer AB and owned Pfizer stock at the time of this study and is at the time of the manuscript submission an employee of AbbVie AB. J. P. T. has been an advisor, Investigator and Speaker for Abbvie, Pfizer, Almirall, LEO Pharma, Sanofi-Genzyme, Eli Lilly & Co and Regeneron. He has received research grants from Sanofi-Genzyme and Regeneron. L. B. v. K. has been consultant or speaker for Pfizer, Sanofi-Genzyme, Leo Pharma and Eli Lilly. K. G. is an employee and board member of Quantify Research and owns Quantify Research stock options. G. O. is an employee of Quantify Research and owns Quantify Research stock options. A. R. D. is an employee of Quantify Research. I. L. was an employee of Quantify Research during the development of this manuscript and is at the time of manuscript submission, an employee of UCB Pharma AB. Quantify Research AB provides consulting and other research services to pharmaceutical, medical device and related organizations. Quantify Research AB received funding from Pfizer Inc. to conduct this study and for the development of this manuscript. The remaining author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data used in this study are protected under Swedish and European law and may only be accessed following relevant ethical approvals, data protection assessments and compliance with GDPR and other legal frameworks.

ETHICS STATEMENT

Ethics approval for the present study was obtained in July 2019 by the Swedish Ethical Review Board (reference number 2019-03840). Individual patient consent was not required according to local law regarding the collection of administrative secondary registry data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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