ORIGINAL RESEARCH

Epidemiology and Economic Burden of Atopic Dermatitis: Real-World Retrospective Data from a Large Nationwide Israeli Healthcare Provider Database

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ABSTRACT

Introduction: Real-world data on the epidemiology and economic burden of atopic dermatitis (AD) are limited. Here we describe the epidemiology and economic burden of AD using electronic healthcare data from Israel.

Methods: A retrospective study was performed using the Maccabi Healthcare Services database. AD incidence in 2008–2017 and point prevalence (AD_{prev}) on 31 December 2017 were described using diagnosis codes for overall patients, and sex and age subgroups. For AD_{prev}, severity was defined using recently dispensed treatments for AD. Annual healthcare resource utilization in AD prevalent patients was compared with non-AD matched controls using generalized linear modelling. Direct annual costs were estimated also.

Results: AD incidence was 7.0/1000 person-years; overall prevalence was 4.4% (female patients 4.5%, male patients 4.3%; age 0 to less than 6 months, 0.9%; 6 months to less than 12 years, 11.0%; 12 to less than 18 years, 5.8%; 18 years or older, 2.2%). Among AD_{prev} ($n = 94,483$), mild, moderate, and severe AD comprised 57.7%, 36.2%, and 6.1% (adults 43.8%, 46.3%, 9.9%), respectively. Dermatologist and allergist visits and hospitalization rates (at least one) were 40.7%, 6.6%, and 3.8% in 2017. Compared with controls, overall and

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moderate-to-severe AD were associated with 36% and 52% increases in annual per-person costs (incremental costs $126 and $190).
Conclusions: AD epidemiology in Israel is comparable with other real-world database studies. AD imposes an economic burden that increases with disease severity.

PLAIN LANGUAGE SUMMARY

Occurrence and costs of atopic dermatitis in Israel

Atopic dermatitis is a disease that causes the skin to be inflamed and itchy. Atopic dermatitis is most common in children but can also occur in adolescents and adults. Using data from a large healthcare provider in Israel, this study aimed to describe how common atopic dermatitis is within the population. Costs related to the use of healthcare services (such as visits to dermatologists and creams to treat atopic dermatitis) in the year 2017 were compared between persons with versus without atopic dermatitis. For the years 2008 to 2017, approximately 7 out of 1000 people were newly diagnosed with atopic dermatitis each year (incidence). Among people alive on 31 December 2017, 4.4% had atopic dermatitis (prevalence), with 42.3% suggestive of moderate to severe disease. Patients with atopic dermatitis, particularly those with more severe disease, used healthcare services more frequently. Compared with people without atopic dermatitis, medical costs among patients with atopic dermatitis were 36% higher (corresponding to added costs of $126 per person per year). This study helps to better understand how many people have atopic dermatitis, and what healthcare resources are needed to manage this disease.

Keywords: Atopic eczema; Epidemiology; Health economics

Key Summary Points

Why carry out this study?

Real-world data suggest that atopic dermatitis (AD), particularly severe AD, is associated with a high comorbidity burden, healthcare resource utilization, and healthcare costs.

To date, limited data are available on the burden of AD in Israel.

This study describes the epidemiology and economic burden of AD in a large population in Israel.

What was learned from the study?

Using real-world data, we estimated an incidence of AD in Israel of 7.0/1000 person-years. Prevalence of AD was 4.4%, with 42.3% suggestive of moderate-to-severe AD. AD was associated with an added economic burden, which increased with disease severity.

This study may help inform decisions for appropriate healthcare resourcing.

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory disease with a complex pathogenesis and significant physical, psychological, and economic burden [1–5]. AD is usually diagnosed in childhood, with approximately 85% of cases diagnosed before 5 years of age [6]. Many patients develop persistent AD [7].

The lifetime prevalence of AD is reported to be 15–30% in children and 2–10% in adults [1, 8], with an increased incidence in recent decades in industrialized countries [9]. Real-

world data suggest that AD, particularly severe AD, is associated with a high comorbidity burden, healthcare resource utilization (HCRU), and healthcare costs [10–13]. However, our understanding of the burden of AD is limited by methodological differences in AD patient identification across studies [8, 14], as well as challenges in capturing patients' HCRU in inpatient and outpatient settings. In addition, limited data are available on the burden of AD in Israel, and up-to-date epidemiological data are valuable as the AD treatment landscape evolves.

This study aimed to describe the epidemiology of AD over a 10-year period and estimate the economic burden of AD using data from a large nationally representative healthcare database in Israel.

METHODS

Data Source

A retrospective database study was conducted with Maccabi Healthcare Services (MHS), a nationwide healthcare insurer/provider with more than 2.3 million members in 2017, representing approximately a quarter of the population in Israel. The MHS databases integrate routinely collected longitudinal data, computerized since 1998 (annual retention rate, greater than 98%), from the MHS central laboratory, medication prescriptions and purchases throughout the MHS pharmacy network, consultations, hospitalizations, and procedures, and sociodemographic data. The main coding systems used are the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), Current Procedural Terminology, and Israeli medication coding system with translations to the Anatomical Therapeutic Chemical codes.

AD Case Definition

Data were collected on all inpatient and outpatient diagnoses of AD (ICD-9-CM 691.8) from 1998 to 2017. The diagnosis date was defined by the earliest diagnosis during this period.

Patients diagnosed with AD were required to meet at least one of the following criteria:

(a) Diagnosis (at least one) from a relevant specialist in dermatology or immunology/allergy

(b) Diagnosis (at least one) given in a hospital or an MHS Medication Approval Centre (linked to medications requiring prior approval) or flagged by a physician as a chronic/recurrent (active) condition

(c) Diagnoses (at least two separate) from a primary care physician (PCP), including pediatricians and general practitioners

(d) Diagnosis (at least one) from a PCP or other related specialists combined with a dispensed prescription of topical calcineurin inhibitors (TCIs; indicated for patients with AD only within the Israeli national basket of health services).

Study Populations

Incidence Population

The incidence of newly diagnosed AD was described over a 10-year period (2008–2017). Incident patients had their earliest AD diagnosis date between 2008 and 2017, with at least 12 months of continuous health plan enrolment before the AD diagnosis date (except for patients diagnosed with AD before age 12 months, in order to capture newly diagnosed infants). This baseline enrolment period was intended as a "washout" period to exclude potential prevalent patients. The population was categorized into the following age groups: less than 6 months, 6 months to less than 12 years, more than 12 years to less than 18 years, and 18 years or older to investigate the incidence of AD in infants less than 6 months of age, children, adolescents, and adults in accordance with pediatric and adolescent age groups commonly used in large epidemiological studies [15].

Prevalence Population

The point prevalence of AD was described among MHS members alive on 31 December 2017 whose AD diagnosis date occurred

between 1998 and 2017 and who had a diagnosis code for AD in the past 5 years (2013–2017) to classify their disease as recent or active. Continuous health plan enrolment from 1 January 2017 was required (except for infants born in 2017) in order to capture data on patient characteristics and annual HCRU. The prevalence population was categorized into the same age groups as the incident population.

Non-AD Controls
The non-AD control population was drawn from the general population of MHS members alive on 31 December 2017 who had no prior AD diagnosis and met the same enrolment criteria as the AD prevalence population. Controls were individually matched (1:1) to patients from the AD prevalence population by age (by birth year, except for infants born in 2017 who were split into 0 to less than 6 months and 6 to less than 12 months), sex, and residential area.

Study Variables and Definitions

Sociodemographic Characteristics
Patients were characterized by age, sex, residential area, and socioeconomic status (SES). SES was based on a score ranked from 1 (lowest) to 10 on an individual's residence place (at the neighborhood level) [1, 2]. This residential SES measure was originally derived by the Israel Central Bureau of Statistics using national census data and augmented by POINTS location profiling Ltd., using aggregated data on housing prices, motorization level, education, employment, and financial resources [16, 17].

AD-Related Treatments
Data were obtained on AD-related treatments dispensed in 2013–2017 (dispensed on/after AD diagnosis date and up to 5 years before AD point prevalence assessment), including topical corticosteroids (TCS) of low/mid/high potency, TCI, systemic corticosteroids (SC), systemic immunomodulators (SI: methotrexate, azathioprine, cyclosporine, mycophenolate mofetil), and phototherapy; biologic therapy for AD was not available in Israel during the study period. TCS potency was defined according to the World Health Organization (WHO) classification, adapted to Israeli guidelines.

Severity
In the AD prevalence population, recently dispensed AD-related treatment data were used as a surrogate for disease severity: moderate AD was defined as at least two separate purchases of TCI or TCS of mid/high potency, or at least one phototherapy; severe AD as at least two SC with moderate AD criteria, or at least one SI; the remainder were defined as mild AD. The severity definition was therefore based on the maximum severity associated with dispensed treatments in the past 5 years. SC were included in the criteria for severe AD because they remain widely prescribed in the routine treatment of moderate to severe AD, despite clinical practice guidelines that largely discourage their use [18].

Healthcare Resource Utilization
Healthcare resource utilization was described for the year 2017 based on the frequency of physician (PCP and specialist [allergy/immunology, dermatology, other]) visits, emergency room visits, hospitalization, dispensed AD-related treatments, and phototherapy.

Direct Medical Costs
Direct medical costs were estimated from the health system perspective using unit costs from the Israeli Ministry of Health price list (2017). Costs were converted to 2017 US dollars, accounting for purchasing power parity [19].

Statistical Analyses

Patient Characteristics
Among the AD prevalence population (overall and by severity) and non-AD controls, descriptive statistics were presented (*n*, percentage; median with interquartile range [IQR]) and differences in patient characteristics across groups were evaluated using χ^2 or Kruskal–Wallis tests. For comparisons of SES across groups, standardized mean difference (SMD) was calculated.

Incidence and Prevalence Rates

To calculate age/sex-specific incidence rates, the number of newly diagnosed patients with AD in each age/sex group and calendar year was divided by the sum of person-years at risk in the corresponding age/sex group and year. The denominator was based on the number of MHS members with at least 12 months of continuous enrolment (unless younger than 12 months old) and no documented diagnosis of AD. Average annual incidence rates in 2008–2017 were reported. To calculate overall and age/sex-specific prevalence rates, the AD prevalence population in each age/sex group was divided by the total population of MHS members on 31 December 2017 (with at least 12 months' prior enrolment, except for infants born in 2017) in the corresponding age/sex group. Fisher's 95% confidence intervals (CI) were calculated for incidence and prevalence rates. Age-standardized incidence and prevalence using the WHO world standard population was also reported [20, 21].

HCRU

Annual utilization rates were summarized as the number (percentage) of patients who used a given healthcare resource at least once in 2017. Among those who used a given resource, median (interquartile range [IQR]) quantity (e.g., number of visits) used per person was described.

Cost Analyses

In order to account for skewed distributions of costs, a generalized linear model (adjusted for age, sex, and residential area) with log-link function and gamma distribution was used to estimate mean total direct medical costs per person and compare (a) the prevalent AD population versus age- and sex-matched non-AD controls, and (b) between AD cohorts with different AD severity. Patients with extreme costs (top 1% of the distribution) were considered outliers and excluded from this analysis. If one individual in a pair was among the highest cost outliers, then both individuals were excluded.

Analyses used SPSS® v.25 and R statistical software v.3.5. This study using existing (retrospective) data/questionnaires was approved by the Maccabi Research Committee and institutional review board of Bayit Balev Hospital, Israel (0094-18-BBL). The study was conducted in accordance with the principles of the Helsinki Declaration and guidelines for medical research in humans.

RESULTS

Incidence

Newly diagnosed patients with AD ($N = 119{,}826$) were identified between 2008 and 2017 (Supplementary Material, Fig. S1). Patients aged less than 6 months, 6 months to less than 12 years, 12 to less than 18 years, and 18 years or older accounted for 13.4%, 54.0%, 4.4%, and 28.2% of incident cases, respectively. The proportion of patients whose first diagnosis was given by a dermatologist increased with age: 24.7%, 52.9%, 75.6%, and 77.2%, respectively.

The crude incidence of AD was 7.0 (95% CI 7.0–7.0) per 1000 person-years (age-adjusted, 6.9/1000 person-years). Age-specific rates were highest in the less than 6 months group, in which rates per 1000 person-years were significantly higher among male (83.1 [95% CI 81.5–84.8]) versus female (57.3 [95% CI 55.9–58.8]) infants (Fig. 1). Incidence in children aged 0 to 5 years was 39.2/1000 person-years. Age-specific incidence rates by year are included in Supplementary Material Fig. S2.

Prevalence and Severity

AD prevalent patients ($n = 94{,}483$) had a median (IQR) age of 11.2 (5.7–28.4) years (52.3% female). Patients aged less than 6 months, 6 months to less than 12 years, 12 to less than 18 years, and 18 years or older accounted for 0.2%, 52.6%, 13.7%, and 33.5% of prevalence cases, respectively (Table 1, Supplementary Material Table S1). Patients with AD had significantly higher SES compared with non-AD controls ($P < 0.001$); patients with severe AD had relatively lower SES ($P < 0.001$).

The overall AD prevalence was 4.4% (95% CI 4.4–4.4%), and was significantly ($P < 0.05$)
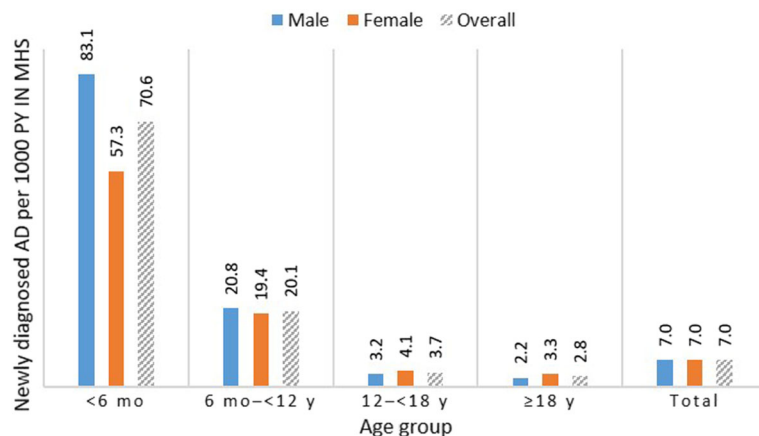
Fig. 1 Atopic dermatitis: age- and sex-specific incidence in Israel* (2008–2017 average). *AD* atopic dermatitis, *MHS* Maccabi Healthcare Services, *mo* months; *y* years. *MHS is a nationwide healthcare insurer and provider with more than 2.3 million members in 2017

Table 1 Characteristics of the AD prevalence population and non-AD matched controls (31 December 2017)

Characteristics	AD vs non-AD matched controls		AD severity		
	AD overall (*n* = 94,483)	Non-AD controls (*n* = 94,483)	Mild (*n* = 54,525)	Moderate (*n* = 34,217)	Severe (*n* = 5741)
Age,* median (IQR), years	11.2 (5.7–28.4)	11.2 (5.7–28.4)	9.4 (5.1–18.3)	14.6 (6.9–36.4)	24.9 (6.6–53.8)
Sex,* %					
Female	52.3	52.3	50.5	55.0	53.4
Male	47.7	47.7	49.5	45.0	46.6
Residential area,* %					
Central	68.1	68.1	66.9	71.0	62.9
North	17.1	17.1	17.5	15.9	19.8
South	14.8	14.8	15.6	13.1	17.4
SES,† %					
Low	17.7	22.6	18.4	16.3	19.1
Medium	33.3	34.4	33.3	33.2	34.8
High	48.9	42.9	48.2	50.5	46.0
Missing	0.1	0.1	0.1	0.0	0.0

AD atopic dermatitis, *IQR* interquartile range, *SES* socioeconomic status

*Variables used for individual matching of patients with AD vs non-AD controls

†SES differed significantly between patients with AD vs non-AD controls ($P < 0.001$; standardized mean difference = 0.145)
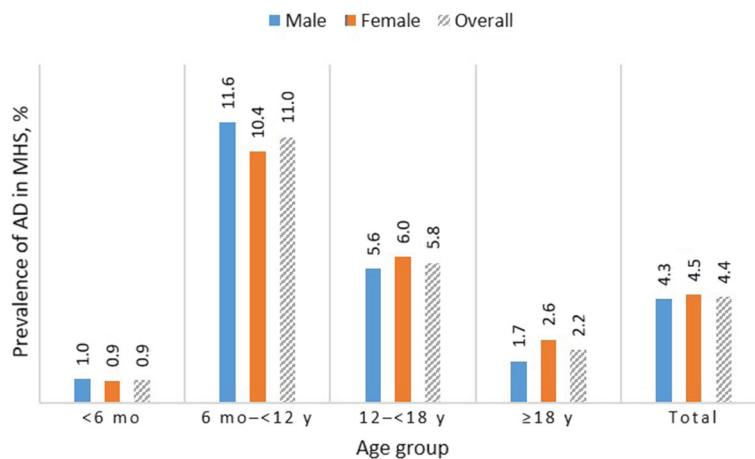
Fig. 2 Atopic dermatitis: age-specific prevalence in Israel* by sex (31 December 2017). *AD* atopic dermatitis, *MHS* Maccabi Healthcare Services, *mo* months, *y* years. *MHS is a nationwide healthcare insurer and provider with more than 2.3 million members in 2017

higher among women (4.5% [95% CI 4.4–4.5%]) versus men (4.3 [95% CI 4.2–4.3%]). Age-specific rates were 0.9%, 11.0%, 5.8%, and 2.2% for those aged less than 6 months, 6 months to less than 12 years, 12 to less than 18 years, and 18 years or older, respectively (Fig. 2). Overall prevalence remained stable (ca. 2%) after 40 years of age (Supplementary Material Fig. S3).

Mild, moderate, and severe disease accounted for 57.7%, 36.2%, and 6.1% of the prevalence population, respectively. The corresponding percentages were 65.9%, 29.6%, and 4.4% among children aged 6 months to less than 12 years; 59.7%, 32.7%, and 3.1% among adolescents 12 to less than 18 years; and 43.8%, 46.3%, and 9.9% among adults. AD-related treatment patterns that defined severity are reported in Supplementary Material Table S1 and prevalence rates of mild, moderate, and severe AD in Supplementary Material Fig. S4.

HCRU and Costs

Eligible patients (*n* = 93,432) were included in the economic burden analysis of the prevalence population by severity. For comparisons to non-AD controls, 92,632 matched pairs were eligible after the highest cost outliers and paired counterparts were excluded. Patients with AD had higher healthcare visit rates and medication use compared with controls (Fig. 3). Overall and across age groups, patients with AD had a significantly higher frequency of PCP visits (overall patients with at least one visit, 94.0% vs 87.9%; median [IQR] number of visits, 6 [3–11] vs 5 [3–9]; $P < 0.001$). Dermatologist and allergist visits and hospitalization rates (at least one) were 40.7%, 6.6%, and 3.8% in 2017. HCRU rates generally increased with increasing AD severity.

Total (unadjusted) annual direct costs were higher in patients with AD versus non-AD controls (Supplementary Material Figs. S5A, B). Compared with non-AD matched controls, overall and moderate-to-severe AD were associated with 36.3% and 52.4% increases in estimated mean per-person costs (incremental costs $125.8 and $190.4), respectively (Table 2; Supplementary Material Fig. S5B).

DISCUSSION

This study provides real-world evidence of the epidemiology and economic burden of mild, moderate, and severe AD in Israel. Our findings indicate that AD incidence (7.0/1000 person-years) and prevalence (4.4%) in this Israeli population are comparable to estimates from other database studies in developed countries. Furthermore, this study indicates that patients with AD had higher HCRU rates and estimated
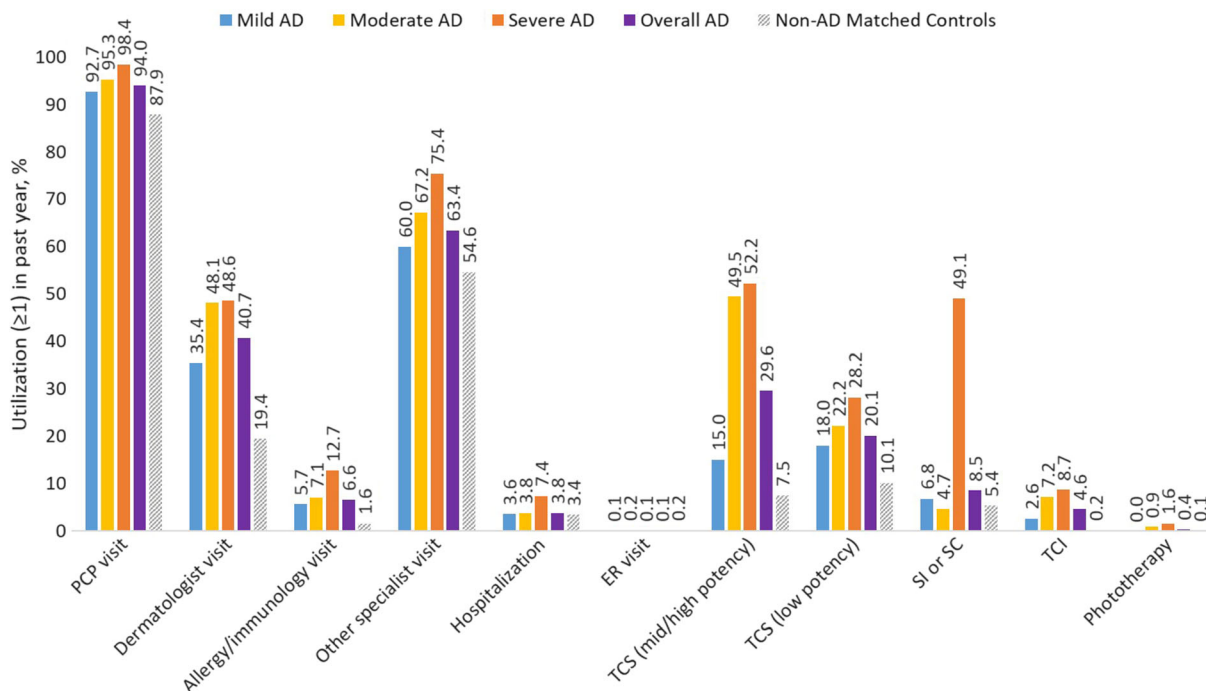
Fig. 3 Atopic dermatitis: HCRU in past year among AD prevalent patients (by severity)* and non-AD controls.† Note that high cost outliers were excluded. *AD* atopic dermatitis, *ER* emergency room, *HCRU* healthcare resource utilization, *PCP* primary care physician, *SI* systemic immunomodulators, *SC* systemic corticosteroids, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroids. *For comparison of AD by severity: $n = 93,432$. † For comparison of AD vs non-AD controls: $n = 92,632$ matched pairs

direct healthcare costs compared with non-AD matched controls, with HCRU and costs generally increasing with disease severity.

Epidemiology of AD

In this Israeli population, we found an AD prevalence of 4.4% in the overall population and 2.2% in adults, which is comparable to other studies using routinely collected health data (median reported prevalence rate, 4.9%) [8]. Prevalence of AD was higher in boys than girls among children younger than 12 but was higher among adult women versus men, consistent with previous studies [22, 23]. In addition, incidence rates among children aged 0 to 5 years were similar to estimates from Denmark and Sweden [24] and Norway [25].

AD Severity and Patient Characteristics

The severity distribution of mild, moderate, and severe AD in our study (57.7%, 36.2%, and 6.1%; adults 43.8%, 46.3%, and 9.9%) was similar to estimates from a Spanish database study among adults with AD that also used a treatment-based severity definition (55.7%, 38.2%, and 6.1%) [26]. The proportion of moderate-to-severe disease in the current study (42.3%; adults 56.2%) was comparable to survey-based estimates from Germany, Japan, the UK [27], and the USA [28]. The relatively lower proportion of AD cases defined as moderate-to-severe in an Israeli study by Shalom et al. (4.2%) [13] likely reflects the use of more stringent treatment-based definitions, which excluded any AD-related treatments not initiated in the same month as the AD diagnosis and did not include TCS or SC.

In the present study, higher SES was associated with increased AD prevalence, whereas

Table 2 Comparisons of estimated direct healthcare costs per person per year among AD prevalence population, by severity, and vs non-AD matched controls (2017)

Comparison	Population	Mean cost, $ (95% CI)	Difference, $ (95% CI)	Cost ratio (95% CI)
Overall AD vs non-AD controls	Non-AD controls	346.6 (344.0–349.3)	Reference	1 (Reference)
N = 92,632 matched pairs	Overall AD	472.4 (468.8–476.1)	125.8 (121.7–129.8)	1.4 (1.4–1.4)
Moderate-to-severe AD vs non-AD controls	Non-AD controls	363.2 (359.0–367.5)	Reference	1 (Reference)
n = 38,847 matched pairs	Moderate-to-severe AD	553.6 (547.2–560.2)	190.4 (183.6–197.2)	1.5 (1.5–1.6)
Moderate or severe AD vs mild AD (n = 93,432)	Mild AD (n = 54,525)	430.6 (426.6–434.5)	Reference	1 (Reference)
	Moderate AD (n = 34,217)	502.1 (496.4–507.8)	71.6 (65.3–77.8)	1.2 (1.2–1.2)
	Severe AD (n = 5741)	757.7 (738.6–777.3)	327.1 (307.6–346.7)	1.8 (1.7–1.8)

Costs are 2017 US dollars; mean per-person costs estimated in generalized linear model adjusting for age, sex, and residential area

AD atopic dermatitis

lower SES was associated with more severe disease. These trends have been reported elsewhere [29]. Chung and Simpson highlight potential explanations for the association between SES and prevalence: increased detection/reporting among families with higher SES (may benefit from increased awareness and/or access to care) and the hygiene hypothesis. Patients with lower SES may have decreased access to healthcare necessary to manage AD, which may contribute to exacerbating disease severity in this population. In addition to direct healthcare costs, patients with AD and their families may be burdened by indirect costs regardless of SES, including absenteeism, lack of concentration, and psychological burden that may affect learning and employment [29, 30].

Economic Burden of AD

Our findings that patients with AD had higher HCRU rates and direct healthcare costs than non-AD matched controls, generally increasing with disease severity, are consistent with recent studies from the USA [12], Singapore.[31], Spain [26], and Israel [13].

Strengths and Limitations

A key strength of this study is the ability to identify and characterize patients with AD using routine healthcare data from multiple sources, including inpatient and outpatient diagnoses and dispensed treatments. Patient-level HCRU data captured in this study allowed for estimation of direct healthcare costs to better understand the economic burden of AD. Nonetheless, several methodological limitations should be considered. As observed with other database studies, sensitivity analyses in our study underscore the challenge of comparing across studies that use different case definitions for AD identification [8, 14]. Removing the inclusion criteria for a recent diagnosis documented in the past 5 years increased the prevalence rate in our population to 7.1% (adults, 3.8%), which is closer to other published real-world estimates of lifetime prevalence [8]. In another sensitivity

analysis, keeping the same time frame as in the main prevalence analysis but expanding the case definition to include at least one AD diagnosis from any source increased prevalence and incidence estimates to 6.1% (adults, 2.7%) and 9.7/1000 person-years, respectively. Previous validation studies of AD algorithms have highlighted the trade-off between sensitivity and specificity in database studies [32]. This trade-off also affects comparisons with a recent Israeli cross-sectional study by Shalom et al., who estimated an AD lifetime prevalence of 2.7% [13], based on a more specific AD algorithm in which diagnoses were given by a dermatologist or during hospitalizations in dermatology departments. Nonetheless, as discussed earlier, incidence and prevalence rates estimated in this study are in line with other database studies from developed countries. Although methodological differences limit our ability to compare estimates from database versus questionnaire studies, adult AD prevalence was also similar to estimates from Germany, Japan, and the UK (2.1–2.5%) [27]. A validation study with chart review could potentially improve AD identification methods in the future.

This study used dispensed AD-related treatments to estimate disease severity. In particular, moderate-to-severe disease may have been overestimated, given the challenges of differentiating mild from moderate disease. For example, patients with clinically mild AD could potentially have been misclassified as moderate AD based on their TCS and TCI use. In addition, AD-related medications used in other indications (e.g., SC use to treat asthma) may also have led to misclassification of severe AD. To address this limitation, we increased the rigidity of our SC-based criteria for severe AD, requiring these patients to also fulfil the criteria for moderate AD. At the same time, undiagnosed and/or undertreated patients may be underestimated.

Our estimates of economic burden did not capture out-of-pocket costs (e.g., moisturizers, over-the-counter treatments, and alternative medicines) or indirect costs due to productivity loss (e.g., time missed from work or school due to illness) [26, 33–36]. Sciattella et al. estimated that direct nonmedical and indirect costs due to productivity loss accounted for 19.9% and 60.8% of the total annual costs per patient, respectively [35]. Finally, evidence suggests that associated comorbidities may also contribute significantly to the economic burden of AD [12, 26, 37]; the impact of atopic diseases, mental health conditions, and other comorbidities will be further investigated in this study population.

CONCLUSIONS

In the current study, AD incidence was 7.0/1000 person-years, prevalence was 4.4%, with 42.3% of patients having moderate-to-severe AD, prevalence was higher among women than men, and highest prevalence was among children aged 6 months to 12 years. Patients with AD had higher HCRU rates than non-AD matched controls, which generally increased with disease severity. Moderate-to-severe AD was associated with 52% increased direct medical cost per capita compared with non-AD matched controls. While further research is needed to investigate the total costs of treating AD, consideration of the entirety of the AD care pathway may inform appropriate healthcare resourcing related to AD.

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