



ORIGINAL ARTICLE

Demographics, healthcare utilization and drug use in children and adults with atopic dermatitis in Denmark: a population-based cross-sectional study

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Abstract

Background Atopic dermatitis (AD) is a common inflammatory skin condition. While previous publications have examined healthcare expenses, large data regarding patient demographics, healthcare use and drug prescriptions are limited.

Objective To examine demographics, healthcare use and drug prescriptions in children and adults with hospital-diagnosed AD.

Methods Danish nationwide registries were cross-linked to access demographic, healthcare and drug prescription data on children and adults with hospital-diagnosed AD (ICD-10 code L20). The diagnostic code for AD used in this study was validated by reviewing medical charts.

Results We identified 9704 children (time period 1997–2012) and 5558 adults (time period 1997–2007) with hospital-diagnosed AD. The diagnostic code L20 had a positive predictive value of 95%. Among children with AD, a larger proportion came from less resourceful families and had immigrant parents from non-European countries. In adults, we observed an opposite tendency. Topical and systemic antibiotics were used relatively frequent in both children and adults with AD. The use of prednisolone and other systemic anti-inflammatory therapy was substantially higher in adults with AD than in children.

Limitations We were unable to identify and describe patients treated by general and private practitioners.

Conclusion There exist significant differences in social predictors for AD and the use of AD medication between children and adults with hospital-diagnosed AD in Denmark. The diagnostic code for AD appears to be valid in Danish registries.

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Conflicts of interest

Dr. Andersen has received research funding from the Lundbeck Foundation, Aage Bang Foundation and A.P. Møller Foundation. Dr. Thyssen has received research a grant from the Lundbeck Foundation attended advisory boards for Roche and Sanofi-Genzyme and received speaker honorarium from LEO Pharma and Sanofi-Genzyme. Dr. Skov has received speaker honoraria from AbbVie, Pfizer, Janssen-Cilag, and Leo Pharma and is a member of the advisory boards of AbbVie, Pfizer, Janssen-Cilag, Sanofi, Eli Lilly, Celgene and Novartis. Dr. Egeberg has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. This research was performed independently through the authors' academic university and hospital affiliations.

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Introduction

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease which is associated with allergic and psychiatric disease.¹ A dramatic increase in the incidence of AD during the

second half of the 20th century has led to growing children and adult patient populations.^{2,3} While recent studies have estimated the financial burden of AD,^{4,5} insight into demographic and drug prescription data among hospital-treated patients is

limited. For example, the proportion of children with AD that are seen by dermatologists, paediatricians and other specialists in a hospital setting is unknown. Furthermore, it is unclear to what degree immigration status influences the healthcare consumption in the context of AD, and whether an urban/rural gradient exists in AD patients seen at hospitals.^{6,7} Finally, data on the use of topical and systemic therapies in children and adults are currently unavailable. In the light of this, better insights into patient demographics along with current therapeutic strategies are needed.⁸

The aim of this register-based study was to provide descriptive data of children and adults with AD seen within a hospital setting in Denmark.

Materials and methods

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736). Approval from the Danish Health Authority was obtained to extract and read patient charts for the validation study (ref. 3-3013-1080/1).

Data sources

All Danish residents have free, equal and universal access to health care provided by the Danish government, including consultations, tests and treatments by general practitioners and in public hospitals. Data collection is an integrated part of health care and social services in Denmark, and nationwide registries provide access to these data for research purposes. The authors of this paper had access to the anonymized databases used in this study. We utilized data from the Danish National Patient Registry, which contains prospectively collected records on all patient contacts at hospital departments (inpatient and ambulatory) as well as few private clinics.⁹ These records include information on time of visit, main and secondary purpose of visit coded by the International Classification of Diseases (ICD). Information regarding physicians within different specialties was also available. In Denmark, dermatologists may be affiliated to a public hospital clinic or work in a private clinic setting. All pharmacy-dispensed prescriptions in Denmark, regardless of prescribing physician, are similarly recorded in the Registry of Medicinal Products Statistics.¹⁰ Information regarding sex, birth date, migration and ethnicity was obtained from the Danish Civil Registration System.¹¹ The Population Education Register contains information on highest completed level of education and the year of completion.¹² The Danish Medical Birth Registry allows for parent-child linkage and contains information on perinatal factors as well as demographic information including maternal municipality of residence.¹³ The data from the registries were cross-linked by a unique identification number that is given to all Danish citizens at birth or migration.

Study design and participants

The study was designed as a matched cross-sectional study in a paediatric and adult population, respectively. In the paediatric cohort, all live-born children born in Denmark between 1 January 1997 and 31 December 2007 served as the source population. All children with a diagnostic code for AD (ICD-10 code group L20) between the date of birth until 31 December 2012 were identified. The paediatric AD population was further stratified into two groups: children who received their first diagnostic code before or after their second birthday. In the adult cohort, we selected all individuals who had received a diagnostic code for AD after their 18th birthday between 1 January 1997 and 31 December 2007. The code had to be the main reason for hospital contact in the adult population. Patients with AD in the paediatric and adult cohorts, respectively, were matched with the same number of controls from the general population based on age and sex at the time of inclusion. In the current study, we utilized the Danish National Patient Registry, where most records originate from public hospitals, although very few are from private clinics. For practical reasons, these patients will henceforth be referred to as hospital-diagnosed patients.

Study outcomes

All study outcomes were defined *a priori*. Outcomes were measured from 1 January 1997 until 30 June 2015 (date of last record in the current dataset). Children who were descendants of immigrants (born by foreign-born parents) were grouped into five major geographical regions based on parental country of origin (Europe and Russia, Africa, Asia, Middle East and North Africa, and the Americas and other). Immigrants (foreign-born individuals) were grouped according to the same regions in the adult cohort. We applied four levels of urbanization which is commonly used in Denmark.¹⁴ Mean tax-reported household income during 5 years prior to study inclusion was calculated and divided into quintiles. The highest completed level of education was divided into seven levels according to the Population Education Register.

In patients with AD, we further identified and quantified healthcare utilization and use of AD-related medications. AD-related prescribed medications included topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), topical antibiotics (fusidic acid, mupirocin and corticosteroids in combination with antibiotics), systemic antibiotics used to treat *Staphylococcus aureus* infection in AD (dicloxacillin and flucloxacillin), topical and systemic antiviral treatment (aciclovir and valaciclovir), methotrexate, azathioprine, cyclosporine and systemic corticosteroids. Mycophenolate mofetil was only relevant in adult patients due to too few prescriptions in paediatric patients. For topical therapies, all preparations were included (creams, ointments etc.). We examined the age at inclusion, main purpose of visit, and the prevalence of TCS and TCI prescriptions in children who received the first AD diagnosis by dermatologists and

paediatricians, respectively. Furthermore, we investigated the number of children with AD who received more than one systemic antibiotic treatment during the study period.

Validation of AD diagnostic code

We randomly selected 100 children and adult patient charts from two hospital-based dermatology clinics in Denmark

Table 1 Demographics of children with atopic dermatitis and general population controls

	Atopic dermatitis <i>n</i> = 9704	Reference group <i>n</i> = 9704	<i>P</i> -values	<i>P</i> for trend
Age at index, median (p25, p75)	2.1 (1.0, 4.4)	2.1 (1.0, 4.4)	n/a	n/a
Age categories in years, <i>n</i> (%)				
<i>x</i> < 1	2364 (24.2)	2364 (24.2)	n/a	n/a
1 ≤ <i>x</i> < 2	2311 (23.7)	2311 (23.7)		
2 ≤ <i>x</i> < 5	3007 (30.8)	3007 (30.8)		
5 ≤ <i>x</i> < 10	1631 (16.7)	1631 (16.7)		
<i>x</i> ≥ 10	443 (4.5)	443 (4.5)		
Gender, <i>n</i> (%)				
Girls	4190 (43.0)	4190 (43.0)	n/a	n/a
Boys	5566 (57.0)	5566 (57.0)		
Ethnicity, <i>n</i> (%)				
Danish	8478 (86.9)	8820 (90.4)	<0.001	n/a
Descendant of immigrant	1275 (13.1)	928 (9.5)		
1) Europe and Russia	266 (2.7)	332 (3.4)		
2) Africa	313 (3.2)	160 (1.6)		
3) Asia	534 (5.5)	254 (2.6)		
4) Middle East and North Africa	153 (1.6)	180 (1.9)		
5) Americas and other	12 (0.1)	10 (0.1)		
Type of municipality, <i>n</i> (%)				
Urban	4930 (50.8)	4871 (50.0)	<0.001	0.333
Intermediate	1285 (13.2)	1485 (15.3)		
Rural	2857 (29.4)	2552 (26.3)		
Remote	591 (6.1)	772 (8.0)		
Missing	41 (0.4)	47 (0.5)		
Household income level, <i>n</i> (%)				
Lowest	2103 (21.7)	1778 (18.3)	<0.001	<0.001
Below average	2010 (20.7)	1872 (19.3)		
Average	1909 (19.7)	1973 (20.3)		
Above average	1837 (18.9)	2045 (21.1)		
Highest	1845 (19.0)	2036 (21.0)		
Maternal age at birth of child, mean (SD)	29.3 (4.9)	29.8 (4.8)	<0.001	n/a
Maternal educational level at index, <i>n</i> (%)				
Primary school (6 years)	100 (1.1)	85 (0.9)	<0.001	<0.001
Middle school (10 years)	1976 (22.0)	1858 (19.8)		
High school and vocational school	3990 (44.5)	4192 (44.7)		
Short higher education	390 (4.4)	449 (4.8)		
Bachelor degree	1891 (21.1)	2050 (21.9)		
Master degree	575 (6.4)	701 (7.5)		
Ph.D. and research fellowships	18 (0.2)	23 (0.3)		
Missing	816 (8.4)	268 (4.1)		
Number of children from same mother, <i>n</i> (%)				
1	2267 (23.4)	2427 (25.0)	<0.001	<0.001
2	4517 (46.6)	4510 (46.5)		
3	2156 (22.2)	2104 (21.7)		
4	540 (5.6)	506 (5.2)		
5	142 (1.5)	107 (1.1)		
≥6	82 (0.9)	50 (0.5)		

Table 1 Continued

	Atopic dermatitis <i>n</i> = 9704	Reference group <i>n</i> = 9704	<i>P</i> -values	<i>P</i> for trend
Child number X from the same mother, <i>n</i> (%)				
1st	5579 (57.2)	5636 (57.8)	0.448	0.276
2nd	3105 (31.8)	3072 (31.5)		
3rd	864 (8.9)	869 (8.9)		
4th or higher	208 (2.1)	179 (1.8)		

n/a, not applicable; p25, 25th percentile; p75, 75th percentile; SD, standard deviation.

(Herlev-Gentofte and Bispebjerg-Frederiksberg hospitals) with at least one record of the ICD-10 code L20 between 1 January 2013 and 31 December 2014. The criterion for validity was the use of the term 'atopic dermatitis' in the chart notes without other competing diagnoses at any time. All chart notes written by physicians employed at the two departments were read from first to last visit.

Statistical analysis

Population characteristics were presented as frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. For non-normally distributed continuous variables, the median and interquartile range (IQR) were calculated. Healthcare utilization in the AD populations was measured as binary outcomes and further quantified in incidence rates per 100 person-years with 95% confidence intervals (CI). Rates were calculated based on follow-up time in the entire AD group and among patients who received that particular prescription. In children with AD, we estimated the age at first prescription. Chi-square tests and *t*-tests were performed to compare differences between the groups. Trend tests were applied to assess ordered categorical variables. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed with SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Validation study

Of 100 patients, 55 were female and 45 were male. The median (IQR) age was 17 (7–39) years with a range between 0 and 91 years. There were 52 children <18 years. Five patients were misclassified, that is they were given a diagnostic code for AD, while the chart notes and the clinical descriptions indicated other conditions. Three of the five misclassified patients (51, 57 and 57 years of age) were initially given a code for AD that was later changed to unspecified dermatitis (L30.9). One patient (76 years) was described as having allergic contact dermatitis in the medical chart. The last misclassified patient (17 years) was described as having mucinosis, whereas no notes about AD were

given. This validation study yielded an overall positive predictive value of 95% (98% in children and 92% in adults, respectively).

Demographics and characteristics of children with AD compared with controls

The paediatric source population consisted of 723 555 children. We identified a total of 9704 children with AD and a similar number of matched controls. The median (IQR) age at inclusion was 2.1 (1.0–4.4) years. The age at first AD code was predominantly under 5 years, and only 4.5% of children were recorded the first time after their 10th birthday (Table 1). There were more boys than girls (57.0% vs. 43.9%). A total of 1275 (13.1%) of children with AD were descendants of immigrants, compared to 928 (9.5%) in the reference group. Among such descendants, children of African descent were seen more frequently in the AD group compared with the reference group (3.2% and 1.6%). Similar tendencies were apparent in children with Asian descent (5.5% and 2.6%). Descendants of Middle Eastern and North African immigrants were similarly distributed in the two groups (1.6% and 1.9%). The between-group differences for ethnicity were statistically significant (*P* < 0.001), whereas no significant trend was seen in terms of level of urbanization (*P* for trend = 0.333). Families of children with AD had a lower household income (*P* for trend <0.001), and mothers in the AD group tended to have a lower education compared with the reference group (*P* for trend <0.001). Mothers of children with hospital-diagnosed AD had on average more children than the reference group (*P* for trend <0.001). No significant difference was observed in terms of birth order of the children (*P* = 0.448).

Demographics and characteristics of adults with AD compared with controls

A total of 4 235 374 adults were identified as the source population during study inclusion period. In the adult population, a total of 5558 patients with an AD diagnosis were included. The median (IQR) age at first diagnostic code after their 18th birthday was 29.6 (22.9–41.1) years, with a decreasing number of patients with increasing age (Table 2).

Table 2 Demographics of adults with atopic dermatitis and general population controls

	Atopic dermatitis <i>n</i> = 5558	Reference group <i>n</i> = 5558	<i>P</i> -values	<i>P</i> for trend
Age at index, median (IQR)	29.6 (22.9–41.1)	29.6 (22.9–41.1)	n/a	n/a
Age categories in years, <i>n</i> (%)				
18 ≤ <i>x</i> < 25	1879 (33.8)	1879 (33.8)	n/a	n/a
25 ≤ <i>x</i> < 35	1668 (30.0)	1668 (30.0)		
35 ≤ <i>x</i> < 45	917 (16.5)	917 (16.5)		
45 ≤ <i>x</i> < 55	556 (10.0)	556 (10.0)		
55 ≤ <i>x</i> < 65	357 (6.4)	357 (6.4)		
<i>x</i> ≥ 65	181 (3.3)	181 (3.3)		
Gender, <i>n</i> (%)				
Women	3633 (65.4)	3633 (65.4)	n/a	n/a
Men	1925 (34.6)	1925 (34.6)		
Ethnicity, <i>n</i> (%)				
Danish	5300 (95.4)	4884 (87.9)	<0.001	n/a
Immigrant	207 (3.7)	592 (10.7)		
1) Europe and Russia	111 (2.0)	287 (5.2)		
2) Africa	14 (0.3)	53 (1.0)		
3) Asia	48 (0.9)	150 (2.7)		
4) Middle East and North Africa	22 (0.4)	75 (1.3)		
5) Americas and other	13 (0.2)	28 (0.5)		
Descendant of immigrant	50 (0.9)	74 (1.3)		
Household income level, <i>n</i> (%)				
Lowest	1132 (20.4)	1091 (19.6)	0.568	0.251
Below average	1113 (20.0)	1111 (20.0)		
Average	1127 (20.3)	1096 (19.7)		
Above average	1081 (19.5)	1142 (20.6)		
Highest	1105 (19.9)	1118 (20.1)		
Educational level at index, <i>n</i> (%)				
Primary school (6 years)	8 (0.1)	20 (0.4)	<0.001	<0.001
Middle school (10 years)	1854 (33.4)	1860 (33.5)		
High school and vocational school	2504 (45.1)	2347 (42.2)		
Short higher education	174 (3.1)	174 (3.1)		
Bachelor degree	732 (13.2)	560 (10.1)		
Master degree	210 (3.8)	193 (3.5)		
Ph.d. and research fellowships	8 (0.1)	12 (0.2)		
Missing	53 (1.0)	274 (4.9)		
Educational level last record, <i>n</i> (%)				
Primary school (6 years)	9 (0.2)	28 (0.5)	<0.001	<0.001
Middle school (10 years)	1003 (18.1)	1074 (19.3)		
High school and vocational school	2138 (38.5)	2212 (39.8)		
Short higher education	295 (5.3)	281 (5.1)		
Bachelor degree	1306 (23.5)	1082 (19.5)		
Master degree	713 (12.8)	589 (10.6)		
Ph.D. and research fellowships	50 (0.9)	46 (0.8)		
Missing	53 (1.0)	274 (4.9)		

IQR, interquartile range; n/a, not applicable; SD, standard deviation.

There was a female predominance (65.4%) in the AD group. A lower prevalence of immigrants was observed among patients with AD (3.7%) compared with the reference group (10.7%). There was no significant between-group difference

in terms of household income levels ($P = 0.568$); however, the educational level was significantly higher among adults with AD compared with the reference group, both at index (P for trend <0.001).

Table 3 Patient characteristics in terms of healthcare utilization and use of medication

	Paediatric population			Adult population
	All children with AD <i>n</i> = 9704	First diagnosis before age 2 <i>n</i> = 4675	First diagnosis after age 2 <i>n</i> = 5029	All adults with AD <i>n</i> = 5558
Study inclusion time in years, mean (SD)	10.0 (4.0)	11.7 (3.6)	8.3 (3.6)	12.8 (3.7)
First AD diagnosis by dermatologist	3553 (36.6)	1499 (32.0)	2054 (40.8)	n/a
First AD diagnosis by paediatrician	5639 (58.1)	2955 (63.2)	2687 (53.4)	n/a
First AD diagnosis by other specialty	512 (5.3)	224 (4.8)	288 (5.7)	n/a
Ever received a diagnostic code of AD by dermatologist	4350 (44.8)	1959 (41.9)	2390 (47.5)	n/a
Ever received a diagnostic code of AD by paediatrician	6115 (63.0)	3211 (68.7)	2904 (57.8)	n/a
Ever received a diagnostic code of AD by other specialty	684 (7.1)	316 (6.8)	368 (7.3)	n/a
Referral to dermatologist when first diagnosed by paediatrician	730 (7.5)	421 (9.0)	309 (6.1)	n/a
Time (years) from first ped consultation to derm referral, median (IQR)	0.6 (0.1–2.9)	0.6 (0.1–2.5)	0.9 (0.1–3.4)	n/a
Consultation rate per 100 person-years where AD is the main diagnosis	11.2 (11.0–11.5)	9.7 (9.5–10.0)	13.2 (12.9–13.6)	14.4 (14.2–14.7)
Topical corticosteroids (TCS)				
Ever received a prescription of any TCS	8812 (90.8)	4179 (89.4)	4633 (92.1)	5426 (97.6)
Mild	5377 (55.4)	2669 (57.1)	2708 (53.9)	2535 (45.6)
Moderate	7838 (80.8)	3692 (79.0)	4146 (82.4)	4628 (83.3)
Potent	4694 (48.4)	1961 (42.0)	2733 (54.3)	5022 (90.4)
Very potent	673 (6.9)	236 (5.1)	437 (8.7)	2487 (44.8)
Age at first prescription of any TCS, median (IQR)	1.0 (0.4–2.0)	0.6 (0.4–1.3)	1.5 (0.6–2.8)	n/a
Mild	1.0 (0.4–2.4)	0.6 (0.4–1.4)	1.7 (0.6–3.6)	n/a
Moderate	1.4 (0.6–2.9)	0.9 (0.5–1.7)	2.0 (1.0–3.9)	n/a
Potent	3.0 (1.5–6.4)	2.0 (1.1–5.2)	3.6 (1.9–6.9)	n/a
Very potent	8.0 (4.2–11.9)	7.3 (3.5–11.7)	8.6 (4.7–12.0)	n/a
TCS prescription rate per 100 person-years (among all with AD)	107 (106–107)	105 (104–106)	107 (106–108)	230 (229–232)
Mild	20.2 (19.9–20.4)	17.6 (17.3–18.0)	23.5 (23.0–23.9)	14.6 (14.3–14.9)
Moderate	57.1 (56.6–57.6)	54.3 (54.7–55.0)	57.4 (56.7–58.0)	69.2 (68.6–69.8)
Potent	27.0 (26.7–27.3)	16.9 (16.6–17.3)	40.2 (39.6–40.8)	124 (123–124)
Very potent	1.8 (1.8–1.9)	0.8 (0.8–0.9)	3.1 (3.0–3.3)	22.9 (22.6–23.3)
TCS prescription rate per 100 person-years (among prescription receivers)	117 (116–117)	117 (116–118)	116 (115–117)	231 (230–232)
Mild	35.3 (34.8–35.8)	30.4 (29.8–31.0)	42.0 (41.2–42.9)	32.0 (31.4–32.7)
Moderate	70.7 (70.1–71.3)	58.6 (57.9–59.4)	86.0 (85.1–87.0)	83.1 (82.3–83.8)
Potent	55.4 (54.8–56.1)	39.1 (38.3–39.9)	72.2 (71.2–73.3)	137 (136–138)
Very potent	26.4 (25.2–27.7)	15.8 (14.4–17.3)	34.5 (32.7–36.4)	50.9 (50.1–51.7)
Topical calcineurin inhibitors				
Ever received a prescription	2833 (29.0)	1127 (24.1)	1706 (33.6)	2254 (40.6)
Age at first prescription, median (IQR)	3.1 (1.7–5.8)	2.1 (1.0–4.5)	3.8 (2.2–6.5)	n/a
Prescription rate per 100 person-years (among all with AD)	16.1 (15.9–16.4)	10.5 (10.3–10.8)	23.4 (22.9–23.9)	18.2 (17.9–18.5)
Prescription rate per 100 person-years (among prescription receivers)	53.9 (53.0–54.7)	43.0 (41.9–44.2)	67.6 (66.3–69.0)	45.9 (45.1–46.7)
Topical antibiotic treatment				
Ever received a prescription	7493 (76.8)	3553 (75.9)	3940 (77.6)	4131 (74.3)
Age at first prescription, median (IQR)	2.0 (0.8–4.0)	1.4 (0.5–3.4)	2.4 (1.2–4.4)	n/a
Prescription rate per 100 person-years (among all with AD)	31.6 (31.3–32.0)	24.5 (24.1–24.9)	41.0 (40.4–41.6)	29.4 (29.0–29.8)
Prescription rate per 100 person-years (among prescription receivers)	39.6 (39.1–40.0)	30.9 (30.4–31.4)	50.7 (49.9–51.4)	39.7 (39.1–40.2)
Systemic antibiotic treatment (dicloxacillin, flucloxacillin)				
Ever received a prescription	3561 (36.7)	1572 (33.6)	1989 (39.6)	3444 (62.0)
Age at first prescription, median (IQR)	4.7 (2.4–7.7)	3.9 (1.6–7.3)	5.1 (3.2–8.0)	n/a
Prescription rate per 100 person-years (among all with AD)	8.6 (8.4–8.7)	6.4 (6.2–6.6)	11.3 (11.0–11.7)	20.9 (20.6–21.3)
Prescription rate per 100 person-years (among prescription receivers)	21.7 (21.2–22.2)	17.3 (16.8–17.9)	26.7 (25.9–27.5)	33.7 (33.2–34.3)
Topical antiviral treatment (aciclovir)				
Ever received a prescription	258 (2.7)	128 (2.7)	130 (2.6)	845 (15.2)

Table 3 Continued

	Paediatric population			Adult population
	All children with AD <i>n</i> = 9704	First diagnosis before age 2 <i>n</i> = 4675	First diagnosis after age 2 <i>n</i> = 5029	All adults with AD <i>n</i> = 5558
Age at first prescription, median (IQR)	5.5 (3.0–9.1)	5.5 (2.7–9.5)	5.6 (3.3–8.9)	n/a
Prescription rate per 100 person-years (among all with AD)	0.5 (0.4–0.6)	0.6 (0.5–0.6)	0.4 (0.4–0.5)	3.0 (2.9–3.2)
Prescription rate per 100 person-years (among prescription receivers)	16.7 (15.3–18.3)	17.7 (15.8–19.8)	15.3 (13.2–17.7)	19.7 (18.9–20.6)
Systemic antiviral treatment (aciclovir, valaciclovir)				
Ever received a prescription	725 (7.5)	329 (7.0)	396 (7.9)	1311 (23.4)
Age at first prescription, median (IQR)	5.6 (2.4–10.4)	4.6 (2.0–9.3)	6.4 (2.6–11.0)	n/a
Prescription rate per 100 person-years (among all with AD)	1.8 (1.7–1.8)	1.4 (1.3–1.5)	2.3 (2.1–2.4)	12.3 (12.1–12.6)
Prescription rate per 100 person-years (among prescription receivers)	21.9 (20.9–23.0)	18.1 (16.8–19.4)	26.3 (24.7–28.1)	51.4 (50.4–52.5)
Methotrexate				
Ever received a prescription	70 (0.7)	20 (0.4)	50 (1.0)	388 (7.0)
Age at first prescription, median (IQR)	9.7 (7.6–13.5)	9.4 (7.7–12.5)	10.4 (7.5–14.1)	n/a
Prescription rate per 100 person-years (among all with AD)	0.5 (0.5–0.6)	0.3 (0.2–0.3)	0.9 (0.8–1.0)	5.0 (4.8–5.2)
Prescription rate per 100 person-years (among prescription receivers)	73.3 (67.1–79.9)	68.0 (57.0–80.4)	94.3 (85.0–104.3)	71.0 (68.7–73.4)
Azathioprine				
Ever received a prescription	72 (0.7)	18 (0.4)	54 (1.1)	1012 (18.2)
Age at first prescription, median (IQR)	10.9 (6.6–13.7)	11.1 (6.8–15.1)	10.8 (6.5–13.4)	n/a
Prescription rate per 100 person-years (among all with AD)	0.9 (0.8–0.9)	0.3 (0.3–0.4)	1.6 (1.5–1.7)	15.2 (14.9–15.5)
Prescription rate per 100 person-years (among prescription receivers)	121 (113–130)	94.5 (81.5–109)	132 (122–142)	82.5 (81.0–84.1)
Cyclosporine				
Ever received a prescription	37 (0.4)	10 (0.2)	27 (0.5)	278 (5.0)
Age at first prescription, median (IQR)	8.3 (6.0–10.6)	7.1 (5.3–8.8)	8.3 (6.2–10.6)	n/a
Prescription rate per 100 person-years (among all with AD)	0.5 (0.4–0.5)	0.23 (0.19–0.27)	0.78 (0.69–0.86)	6.79 (6.60–6.99)
Prescription rate per 100 person-years (among prescription receivers)	124 (103–148)	112 (102–123)	163 (145–181)	127 (124–131)
Systemic corticosteroids				
Ever received a prescription	482 (5.0)	195 (4.2)	287 (5.7)	3196 (57.5)
Age at first prescription, median (IQR)	8.2 (4.6–12.7)	7.9 (3.9–12.3)	8.7 (5.0–12.1)	n/a
Prescription rate per 100 person-years (among all with AD)	1.2 (1.2–1.3)	0.8 (0.7–0.9)	1.8 (1.7–1.9)	35.7 (35.3–36.2)
Prescription rate per 100 person-years (among prescription receivers)	23.6 (22.2–24.9)	17.4 (15.8–19.2)	28.5 (26.5–30.7)	61.4 (60.7–62.2)
Mycophenolate				
Ever received a prescription	na	na	Na	54 (1.0)
Prescription rate per 100 person-years (among all with AD)	na	na	Na	1.2 (1.1–1.3)
Prescription rate per 100 person-years (among prescription receivers)	na	na	Na	121 (123–129)

Events are presented as frequencies and percentages. Rates are presented as events per 100 person-years and 95% confidence intervals.

AD, atopic dermatitis; IQR, interquartile range; n/a, not applicable; SD, standard deviation; TCS, topical corticosteroids.

Healthcare consumption and therapies in children and adults with AD

Overall, children more frequently received their first recorded diagnosis of AD by paediatricians (58.1%) followed by dermatologists (36.6%) and other specialists (5.3%) as seen in Table 3. Children with a first-time AD diagnosis given by a paediatrician were younger compared with children with first-time diagnosis by a dermatologist and had overall lower prevalence of TCS and TCI prescriptions (Table 4). Children who were seen first by a paediatrician were also more likely to have AD as a secondary diagnosis compared with children seen by dermatologists (58.3% vs. 9.3%).

Topical corticosteroids were the most common prescriptions in children with AD (90.8%). In children diagnosed after age two, the prevalence of potent TCS (e.g. betamethasone) was 54.3% with a median age (IQR) at first prescription of 3.6 (1.9–6.9) years and a prescription rate (95% CI) of 72.2 (71.2–73.3) per 100 person-years. Very potent TCS (e.g. clobetasol) were prescribed to fewer (8.7%) and older children [median age (IQR) 8.6 (4.7–12.0)] with a prescription rate (95% CI) of 34.5 (32.7–36.4) per 100 person-years. Systemic dicloxacillin was prescribed in 3561 (36.7%) children with AD, of whom 1784 (18.4%) received two or more prescriptions. Systemic anti-inflammatory therapies were rarely used in children with AD

Table 4 Characteristics of children with a first-time diagnosis by a dermatologist or paediatrician, respectively

	Dermatologist <i>n</i> = 3553	Paediatrician <i>n</i> = 5639
Age at first diagnosis		
<i>x</i> < 1	781 (21.9)	1468 (26.0)
1 ≤ <i>x</i> < 2	715 (20.1)	1483 (26.3)
2 ≤ <i>x</i> < 5	1133 (31.9)	1708 (30.3)
5 ≤ <i>x</i> < 10	700 (19.7)	815 (14.5)
<i>x</i> ≥ 10	224 (6.3)	165 (2.9)
TCI		
Any TCS	1373 (38.6)	1416 (25.1)
Mild TCS	3342 (94.1)	5036 (89.3)
Moderate TCS	2117 (59.6)	3041 (53.9)
Potent TCS	3083 (86.8)	4375 (77.6)
Very potent TCS	2010 (56.6)	2452 (43.5)
Primary diagnosis	304 (8.6)	332 (5.9)
Secondary diagnosis	3223 (90.7)	2352 (41.7)
	330 (9.3)	3287 (58.3)

The column 'Dermatologist' represents children who received their first diagnostic code for atopic dermatitis by a dermatologist. The column 'Paediatrician' represents children who received their first diagnostic code for atopic dermatitis by a paediatrician. The prevalence of ever receiving a prescription is presented as absolute numbers and percentages. Primary and secondary diagnoses indicate whether AD was the main purpose of visit or not. TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

(Table 3). Additional analysis of pharmacotherapy use and hospital visits in children with AD according to the age cut-offs <6, 6–11 and 12–17 years is available in Table 5. The age groups represent the age at first AD diagnosis.

The mean (SD) follow-up time in adults with AD was 12.8 (3.7) years. The consultation rate (95% CI) was higher in adults [14.4 (14.2–14.7) per 100 person-years] compared with children with AD [11.2 (11.0–11.5) per 100 person-years], as were the prevalence and rate of the majority of prescribed medications, apart from mild TCS. The most commonly used systemic anti-inflammatory agent was azathioprine in adults (18%) followed by methotrexate (7.0%), cyclosporine (5.0%) and mycophenolate mofetil (1.0%). Systemic corticosteroids were prescribed to 57.5% of the adults with AD, with a prescription rate (95% CI) of 35.7 (35.3–36.2) per 100 person-years.

Discussion

Main findings

We observed more boys than girls with hospital-diagnosed AD, but a female predominance in adult patients. Children with AD came from less resourceful families than controls and their parents more frequently had immigrant status, while the trend was opposite for adult patients with AD. Patients who received their first diagnostic code by a paediatrician were younger and received fewer drugs than patients seen first by a dermatologist. Topical and systemic antibiotics were used relatively frequent in

Table 5 Characteristics of children with atopic dermatitis according to different age cut-offs

	Age <6 years <i>n</i> = 8184	Age 6–11 years <i>n</i> = 1354	Age 12–17 years <i>n</i> = 166
TCI	2413 (29.5)	475 (35.1)	63 (38.0)
Any TCS	7410 (90.5)	1243 (91.8)	159 (95.8)
Mild TCS	4603 (56.2)	684 (50.5)	90 (54.2)
Moderate TCS	6585 (80.5)	1108 (81.8)	145 (87.4)
Potent TCS	3822 (46.7)	755 (55.8)	117 (70.5)
Very potent TCS	509 (6.2)	137 (10.1)	27 (16.3)
Methotrexate	57 (0.7)	12 (0.9)	n/a
Azathioprine	48 (0.6)	17 (1.3)	7 (4.2)
Cyclosporine	26 (0.3)	9 (0.7)	n/a
Mycophenolate	6 (0.1)	n/a	n/a
Oral antibiotics (flucloxacillin and dicloxacillin)	2903 (35.5)	578 (42.7)	80 (48.2)
Antidepressants	148 (1.8)	44 (3.3)	11 (6.6)
Anxiolytics	555 (6.8)	99 (7.3)	12 (7.2)
Antihistamines	5108 (62.4)	864 (63.8)	116 (69.9)
Inhalants	5117 (62.5)	775 (57.2)	87 (52.4)
Consultation rate per 100 person-years	9.3 (9.2–9.5)	14.0 (13.3–14.8)	21.6 (18.7–25.0)
Hospitalization rate per 100 person-years	1.8 (1.7–1.9)	1.2 (1.0–1.5)	1.4 (0.7–2.6)

The prevalence of ever receiving a prescription is presented as absolute numbers and percentages. The age represents the time of first AD diagnosis. The consultation rate and hospitalization rate represent outpatient and inpatient visits where atopic dermatitis was the main purpose of visit. Numbers <3 could not be presented due to data protection policies and were replaced by n/a.

TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

both children and adults with AD. The use of systemic anti-inflammatory therapy was substantially higher in adults with AD than in children.

Interpretation

More than half of adult AD patients received at least one prescription of systemic corticosteroids during the study period although they carry a risk of a range of harmful side-effects.¹⁵ In a recent consensus paper, AD experts agreed that these should generally be avoided and only used under special circumstances.¹⁶ While we were unable to distinguish the indication for use, and some systemic corticosteroids were possibly prescribed to treat, for example asthma or allergic rhinitis, the results emphasize that physicians generally may tend to prescribe these drugs more than it is indicated. Furthermore, topical and systemic antibiotic therapies were frequently prescribed in both children and adults with AD. It is well established that colonization with *S. aureus* plays an important role in AD pathogenesis; however, the clinical benefits of using antimicrobial treatment in

addition to anti-inflammatory treatment in non-severely infected AD remain unclear.¹⁷

We observed a shift in the gender distribution, with more boys with AD in the paediatric cohort and more women in the adult cohort. A number of birth-cohort studies have shown that male infants carry a higher risk of AD than females.^{18–22} The current understanding of gender distribution in adults with AD is limited; however, high-risk occupations in terms of hand eczema (e.g. nurses or hairdressers) and an overall increased healthcare-seeking behaviour could contribute to the observed high prevalence of women in our AD cohort.

Parental socio-economic and educational levels were lower in children with AD compared to controls, while educational level was higher in adults with AD. We normally assume that patients treated within the hospitals system, rather than in primary and secondary care, represent those with severe AD.²³ However, other factors may also influence the referral patterns from primary care, such as lower treatment adherence in less resourceful families leading to persistent disease, language barriers and higher demands by affluent families. Danish hospital clinics offer eczema schools, longer consultations, translation services and patient information. Dermatology-related emergency department visits and hospitalizations for AD have previously been associated with racial/ethnic minorities and lower socio-economic levels in the United States, indicating that social disparities are present in dermatologic care in hospital settings.^{24,25}

We observed a higher proportion of children with immigrant parents in the AD group, which could be partially linked to level of deprivation. Furthermore, studies have shown that children with immigrant parents who are born in western countries have a higher risk of atopic diseases compared with foreign-born children.^{26–29} Healthcare utilization in immigrants may vary greatly depending on country of origin. A Norwegian study found significant variations in healthcare utilization between immigrants from four different countries in sub-Saharan Africa, and the use of primary health care reduced with longer duration of stay in Norway.³⁰ In our study, children with parents from Middle Eastern and North African descent did not have an increased prevalence of AD, which could be explained by differences in genetic predisposition.³¹ We observed fewer immigrants in adults with AD, possibly due to a lower risk of AD in their country of origin, or because their earlier symptoms of AD had resolved at the time of immigration.

No urban/rural gradient regarding prevalence of hospital-diagnosed AD was observed in children, contrasting results from a systematic review article that found evidence of a higher risk of AD in urban areas,³² as did a recent Danish birth-cohort study including approximately 50 000 children.²² Denmark is a relatively small and homogenous country with short distances, and it is indeed possible that patients who are referred to hospital clinics and departments are willing to travel regardless of their area of residency. Also, air pollution has been suggested as a risk

factor or aggravating factor for AD and could be a contributing factor in the urban/rural gradient.³³ Urban areas in Denmark, however, have relatively low concentrations of air pollutants in a global perspective.³⁴

Young adults constituted the largest age group at index in the adult population. The index date did not necessarily represent the age at onset, but the first recorded diagnosis during adulthood. These patients could represent a cohort effect of children growing up in the 1980s and 1990s when the incidence of AD increased dramatically,³⁵ or could indicate a need of referral due to stress factors in this particular susceptible period in life. Finally, anxiety and depression are associated with AD and this occurs frequently in adolescents and young adults.³⁶

Strengths and limitations

This study has several strengths. The large sample size allows for a detailed description of the patient groups. Furthermore, the data were collected prospectively, thereby eliminating the risk of recall bias. The studied populations were, however, a selected group of patients and do not necessarily represent all AD patients in Denmark. Although all filled prescriptions in Denmark are recorded in the registry, we did not have access to information regarding consultations by general practitioners. Mild TCS and topical antiviral medication are available over the counter and were possibly underestimated. We did not have access to the indications of use of medication, and some prescriptions may have been intended to treat other conditions. In terms of disease onset and severity, no specific clinical measures were available. In the validation study, we did not apply validity criteria based on clinical diagnostic criteria, as patient charts are written as free text in Danish hospitals, and the presence or absence of symptoms is not always written in detail. Although we found a high predictive value of the diagnostic code for AD, we cannot rule out the possibility of some misclassification in our paediatric and adult AD cohorts.

Conclusion

In this study of patients with hospital-diagnosed AD in Denmark, we observed significant differences in patient demographics and characteristics in children and adults, respectively. The results suggest that social factors and immigration status are important predictors for hospital referrals and may vary according to the patient's age. We also observed that systemic corticosteroids and antibiotics were prescribed frequently in patients with AD. The diagnostic code for AD had a high positive predictive value, suggesting a low risk of misclassification in the Danish registries.

References

- 1 Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**: 1109–1122.
- 2 Deckers IAG, McLean S, Linssen S *et al*. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–

- 2010: a systematic review of epidemiological studies. *PLoS One* 2012; **7**: e39803.
- 3 Henriksen L, Simonsen J, Haerskjold A et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 2015; **136**: 360–366.e2.
 - 4 Narla S, Hsu DY, Thyssen JP, Silverberg JI. Inpatient financial burden of atopic dermatitis in the United States. *J Invest Dermatol* 2017; **137**: 1461–1467.
 - 5 Ellis CN, Drake LA, Prendergast MM et al. Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol* 2002; **46**: 361–370.
 - 6 Norredam M, Nielsen SS, Krasnik A. Migrants' utilization of somatic healthcare services in Europe—a systematic review. *Eur J Public Health* 2010; **20**: 555–563.
 - 7 Engebretsen KA, Bager P, Wohlfahrt J et al. Prevalence of atopic dermatitis in infants by domestic water hardness and season of birth: cohort study. *J Allergy Clin Immunol* 2017; **139**: 1568–1574.e1.
 - 8 Boguniewicz M, Alexis AF, Beck LA et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract* 2017; **5**: 1519–1531.
 - 9 Andersen TF, Madsen M, Jørgensen J et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–268.
 - 10 Kildemoes HW, Sørensen HT, Hallas J. The Danish national prescription registry. *Scand J Public Health* 2011; **39**: 38–41.
 - 11 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; **29**: 541–549.
 - 12 Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011; **39**: 91–94.
 - 13 Knudsen LB, Olsen J. The Danish medical birth registry. *Dan Med Bull* 1998; **45**: 320–323.
 - 14 REGIONAL-OG LANDDISTRIKTS- POLITISK REDEGØRELSE 2012.
 - 15 Yu S, Drucker AM, Lebwohl M, Silverberg JI. A systematic review of safety and efficacy of systemic corticosteroids in atopic dermatitis. *J Am Acad Dermatol* 2018; **78**: 733–740.e11.
 - 16 Drucker AM, Eyerich K, de Bruin-Weller MS et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *Br J Dermatol* 2018; **178**: 768–775.
 - 17 Francis NA, Ridd MJ, Thomas-Jones E et al. Oral and topical antibiotics for clinically infected eczema in children: a pragmatic randomized controlled trial in ambulatory care. *Ann Fam Med* 2017; **15**: 124–130.
 - 18 Egeberg A, Andersen YMF, Gislason G et al. Neonatal risk factors of atopic dermatitis in Denmark - results from a nationwide register-based study. *Pediatr Allergy Immunol* 2016; **27**: 368–374.
 - 19 Moore MM, Rifas-Shiman SL, Rich-Edwards JW et al. Perinatal predictors of atopic dermatitis occurring in the first six months of life. *Pediatrics* 2004; **113**: 468–474.
 - 20 Böhme M, Svensson A, Kull I, Nordvall SL, Wahlgren CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Derm Venereol* 2001; **81**: 193–197.
 - 21 Trønnes H, Wilcox AJ, Lie RT et al. The association of preterm birth with severe asthma and atopic dermatitis: a national cohort study. *Pediatr Allergy Immunol* 2013; **24**: 782–787.
 - 22 Engebretsen KA, Bager P, Wohlfahrt J et al. Prevalence of atopic dermatitis in infants by domestic water hardness and season of birth: cohort study. *J Allergy Clin Immunol* 2017; **139**: 1568–1574.e1.
 - 23 Egeberg A, Andersen YMF, Gislason GH et al. Differential disease burden and treatment patterns among adults with psoriasis and atopic dermatitis seen in hospital vs. private clinics. *J Eur Acad Dermatol Venereol* 2018; **32**: e23–e25.
 - 24 Narla S, Hsu DY, Thyssen JP, Silverberg JI. Predictors of hospitalization, length of stay, and costs of care among adult and pediatric inpatients with atopic dermatitis in the United States. *Dermatitis* 2018; **29**: 22–31.
 - 25 Jackson C, Maibach H. Ethnic and socioeconomic disparities in dermatology. *J Dermatolog Treat* 2016; **27**: 954–6634.
 - 26 Silverberg JI, Simpson EL, Durkin HG, Joks R. Prevalence of allergic disease in foreign-born American children. *JAMA Pediatr* 2013; **167**: 554–560.
 - 27 Cabieses B, Uphoff E, Pinart M et al. A systematic review on the development of asthma and allergic diseases in relation to international immigration: the leading role of the environment confirmed. *PLoS One* 2014; **9**: e105347.
 - 28 Tedeschi A, Barcella M, Bo GAD, Miadonna A. Onset of allergy and asthma symptoms in extra-European immigrants to Milan, Italy: possible role of environmental factors. *Clin Exp Allergy* 2003; **33**: 449–454.
 - 29 Leung RC, Carlin JB, Burdon JG, Czarny D. Asthma, allergy and atopy in Asian immigrants in Melbourne. *Med J Aust* 1994; **161**: 418–425.
 - 30 Diaz E, Mbanya VN, Gele AA, Kumar B. Differences in primary health care use among sub-Saharan African immigrants in Norway: a register-based study. *BMC Health Serv Res* 2017; **17**: 509.
 - 31 Beasley R. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **351**: 1225–1232.
 - 32 Schram ME, Tedja AM, Spijker R et al. Is there a rural/urban gradient in the prevalence of eczema? A systematic review *Br J Dermatol* 2010; **162**: 964–973.
 - 33 Ahn K. The role of air pollutants in atopic dermatitis. *J Allergy Clin Immunol* 2014; **134**: 993–999.
 - 34 WHO. WHO global urban ambient air pollution database (update 2016). WHO 2017.
 - 35 Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939–45 war. *Lancet* 1984; **2**: 1255–1257.
 - 36 Andersen YMF, Egeberg A, Skov L, Thyssen JP. Comorbidities of atopic dermatitis: beyond rhinitis and asthma. *Curr Dermatol Rep* 2017; **6**: 35–41.