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Prevalence of atopic dermatitis in the adolescent population of Catalonia (Spain)

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Abstract
Background: Studies on the prevalence of atopic dermatitis (AD) for the adolescent cohort in general-based large populations are scarce worldwide. We performed a retrospective population-based observational cohort study of 76,665 adolescent patients diagnosed with AD in Catalonia (Spain). We studied the prevalence of AD by age, gender, disease severity, comorbidities, serum total immunoglobulin E (tIgE) and appropriate medical treatment (AMT) for the Catalan population.
Methods: Adolescent individuals (12-17 years) diagnosed with AD by medical records at different health care levels (primary, hospital, emergency) from the Catalan Health System (CHS) were included. Statistical analyses evaluated sociodemographic characteristics, prevalence, comorbidities, serum tIgE and AMT.
Results: The overall diagnosed AD prevalence in the adolescent Catalan population (76,665) was 16.9%, being higher for the non-severe (16.7%) than for the severe (0.2%) populations. Topical corticosteroids were the most prescribed drug (49.5%), and the use of all prescribed treatments was higher in severe AD patients, especially systemic corticosteroids (49.7%) and immunosuppressants (45.4%). AD patients had, on average, a serum tIgE of 163.6 KU/L, which was higher for severe than non-severe disease (155.5 KU/L vs 101.9 KU/L, respectively). Allergic rhinitis (15.0%) and asthma (13.5%) were among the most frequent comorbid respiratory and allergy diseases.

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Conclusions: This is the first Spanish study reporting the overall diagnosed prevalence for a large-scale adolescent cohort (12–17 years old) from Catalonia. It provides new and robust evidence of AD's prevalence and related characteristics in this region.

Introduction

Atopic dermatitis (AD) is a non-contagious, pruritic inflammatory skin condition with defects in the epidermal barrier. It is chronically relapsing in families with atopic diseases: AD, food allergies, bronchial asthma and/or allergic rhino-conjunctivitis.[1,2]

The pathogenesis of AD is multifactorial, although, in recent years, it has been considered a Type 2 inflammatory disease (T2) characterised by interleukin (IL)-4 signalling.[3,4] The genetic component significantly influences the skin microbiome and environmental factors. AD usually begins in childhood; it is the most common skin disease in children, with a high impact on the individual's quality of life. Infants with AD may develop the *atopic march*, which relates to the subsequent or concomitant development of other atopic disorders, including food allergy, allergic rhinitis, and asthma.[4,5] Severe cases may persist over time and are more often during adulthood.[6]

The epidemiology of AD reports an estimated global prevalence of about 19.8% in the Spanish adolescent population.[7] In Western Europe, 8.8% of adolescents aged 13–14 were estimated to have AD.[8] Prevalence estimates for Spain among the adolescent cohort vary between 4.6[6] and 6.2%[7] for those between 13 and 14 years old, and it is estimated to be 6.4% for those between 13 and 18 years old[9] and 19.8% for adolescents.[7] Prevalence of severe AD is estimated to be 0.23% for adolescents from 13 to 18 years old.[9]

AD is associated with impaired skin barrier function and systemic immune dysregulation, particularly upregulation of type 2 immune pathway.[10] The systemic nature of AD is highlighted by the frequent occurrence of comorbid conditions (including most types of asthma, food allergy, eosinophilic esophagitis and chronic sinonasal conditions such as allergic rhinitis and chronic rhinosinusitis with or without nasal polyps), the pathology of which is characterised by type 2 inflammation.[11]

Our epidemiological study, using a retrospective large-scale population-based database over the period 2013–2017, aims to investigate the diagnosed prevalence, overall and by age and gender, as well as disease severity, comorbidities and undergone medical treatments of an AD cohort of adolescents (12–17 years old) from Catalonia (Spain).

Materials and Methods

Study population

All residents in Catalonia – the second largest populated region in Spain, representing 16.38% of the Spanish population – with coverage in the statutory National Health Service (NHS) and included in the Agency for Health Quality and Assessment of Catalonia (AQuAS) database with the following criteria were analysed. Inclusion criteria: (1) Patients aged 12–17 years and (2) with a diagnosis of AD established by medical records at any care level covered by the NHS (primary, hospital, ambulance and emergency care) at any point in time from January 2013 until December 2017 (follow-up period is different for each individual in the dataset). Exclusion criteria were subjects transferred to other regions in Spain. There were 76,665 adolescents diagnosed with AD over the 2013–2017 study period constituting the population under study.

Data obtained were confidential, anonymous and dissociated according to the Spanish Organic Law on Data Protection (Law 15/1999 of December 13). The Spanish Agency classified the study for Medicines and Health Products as a No-EPA *(i.e. no drug post-authorization) study as this is a* retrospective observational study of *the epidemiological characteristics of AD.* It was approved by the Clinical Research Ethics Committee, International University of Catalonia (Barcelona) and the Ethics Committee from *Hospital Clínic de Barcelona.*

Study design

AQuAS provided the database and contains details of all administrative medical registers on available admissions to primary care, hospital care and ambulance and emergency (A&E) attendances at the individual-patient level of residents in Catalonia with coverage in the NHS.

The AD diagnostic was given in the database using records grounded on medically certified diagnoses coded with the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). ICD-9-CM codes were considered: 691.8 – AD and related states – Other AD and associated conditions: AD, eczema, neurodermatitis; 692.9 – contact dermatitis and another eczema, unknown cause.

The prescribed AD therapies (topical corticosteroids, antihistamines, immunosuppressant agents and systemic corticosteroids) available in the database for the period under study can be found in the supplementary material.

See supplementary material for further description of the database and prescribed treatment codes.

Disease severity

Since symptoms data were unavailable in the dataset and the SCORAD scale,[1,12] the disease severity classification (non-severe, severe) was based on drug prescription following the existing Spanish literature.[9,13]

Each individual's drug prescription over the last 2 years was considered to capture the most updated degree of severity. The adolescent population was classified as

having severe AD disease when: (1) prescription of immunosuppressant agents (ciclosporin, azathioprine, cyclophosphamide, methotrexate, alitretinoin, mycophenolic acid, interferon-alpha-2a and interferon alpha-2b) at least once over the last 2 years or (2) one or more hospitalisations/emergencies over the last 2 years with AD as a first diagnostic. Patients were considered non-severe in all other situations.

Outcomes

Demographic characteristics

Information on socioeconomic and demographic characteristics were obtained: (1) gender, (2) age and (3) annual income levels were constructed and adjusted by household size.

Epidemiology

The overall diagnosed AD prevalence in the general adolescent population was calculated based on all individuals from the study population who received a diagnosis of AD over the total adolescent population in Catalonia (454,659 residents in 2017). Since the database encompasses the entire adolescent population of Catalonia, prevalence results do not represent estimated values. Instead, data should be interpreted as the diagnosed prevalence in Catalonia from 2013 to 2017.

Total serum IgE biomarker

Atopy and its allergic responses are associated with increased serum total immunoglobulin E (tIgE) production.[14] Therefore, tIgE was also provided in the *AQUAS* dataset and was used to calculate the median (confidence interval [CI]) and the number of individuals above and below the cut-off point value (≥100 KU/L were considered as high levels) for the total adolescent population by disease severity and by comorbidities. The maximum value reported for everyone between the 2016 and 2017 study was taken.

Comorbidities

AD comorbidities, including respiratory/allergy and systemic/general, were also analysed and found in the supplementary material for the general adolescent population.

Statistical analysis

An observational, multi-centre, longitudinal retrospective study was performed based on a review of all available medical records related to AD in Catalonia – from 2013 to 2017 using computerised databases with dissociated data.

Statistical analyses were conducted using the statistical package Stata 17. Descriptive analysis was performed by reporting frequencies and proportions of individuals in the overall population and by disease severity for confounders, comorbidities, treatment characteristics and biomarkers. Pearson's chi-square test of independence between categorical variables were reported, as well as mean differences by disease severity. Odds ratio (OR) with 95% CI and p-values were reported for the multivariate logistic regression on the probability of having a severe AD against comorbidities and confounders. The overall prevalence of AD was reported, as well as the prevalence by cohorts and disease severity, all analysed by gender and age groups. A p-value <0.05 was considered statistically significant.

Results

Descriptive characteristics

Most AD cases concentrate during childhood and until 18 years old (Figure 1), hence the importance of the study. After that, the population shrinks, with fewer AD cases in adults.

A total of 76,665 adolescents out of 454,659 residents in Catalonia in 2017 were diagnosed with AD. Among them, 1.03% (782 individuals) were classified as presenting with severe AD, and 98.9% (75,883 individuals) as having non-severe AD (Figure 2).

Compared to boys, a similar number of girls were diagnosed with AD (1.1:1) (Table 1). A slightly higher proportion was found for girls with AD for the severe cohort (1.31:1). More than half (60.5%) of the AD adolescents cohort lived in families with annual incomes <18,000€ (Table 1).

AD prevalence

The diagnosed prevalence of AD for adolescents was 16.9% (76,665 individuals), higher in the non-severe vs severe group (16.7% vs 0.2%). By gender, the overall prevalence was higher for females than males (18.2% vs 15.6%, $p < 0.0001$) in the severe and non-severe groups (Figure 3).

Prescribed treatment

Within the 2013–2017 study period, topical corticosteroids were the most prescribed drugs in the AD population (49.5%) and each severity group (49.2% for non-severe and 76.2% for severe). It was followed by oral antihistamines (43.8%) and systemic corticosteroids (17.6%). All medications were more prescribed in severe than non-severe AD patients; this difference is especially significant for systemic corticosteroids (49.7% vs 17.3%, respectively) and non-steroidal immunosuppressant agents (45.4% vs 4.0%). Around 28.7% of individuals had no prescription for any AD treatment and were considered non-severe (Table 2). See supplementary material for prescribed treatment by adolescent cohorts.

Total serum IgE

During the 2-year period (2016–2017), there were 18,454 individuals with available information on serum tIgE.

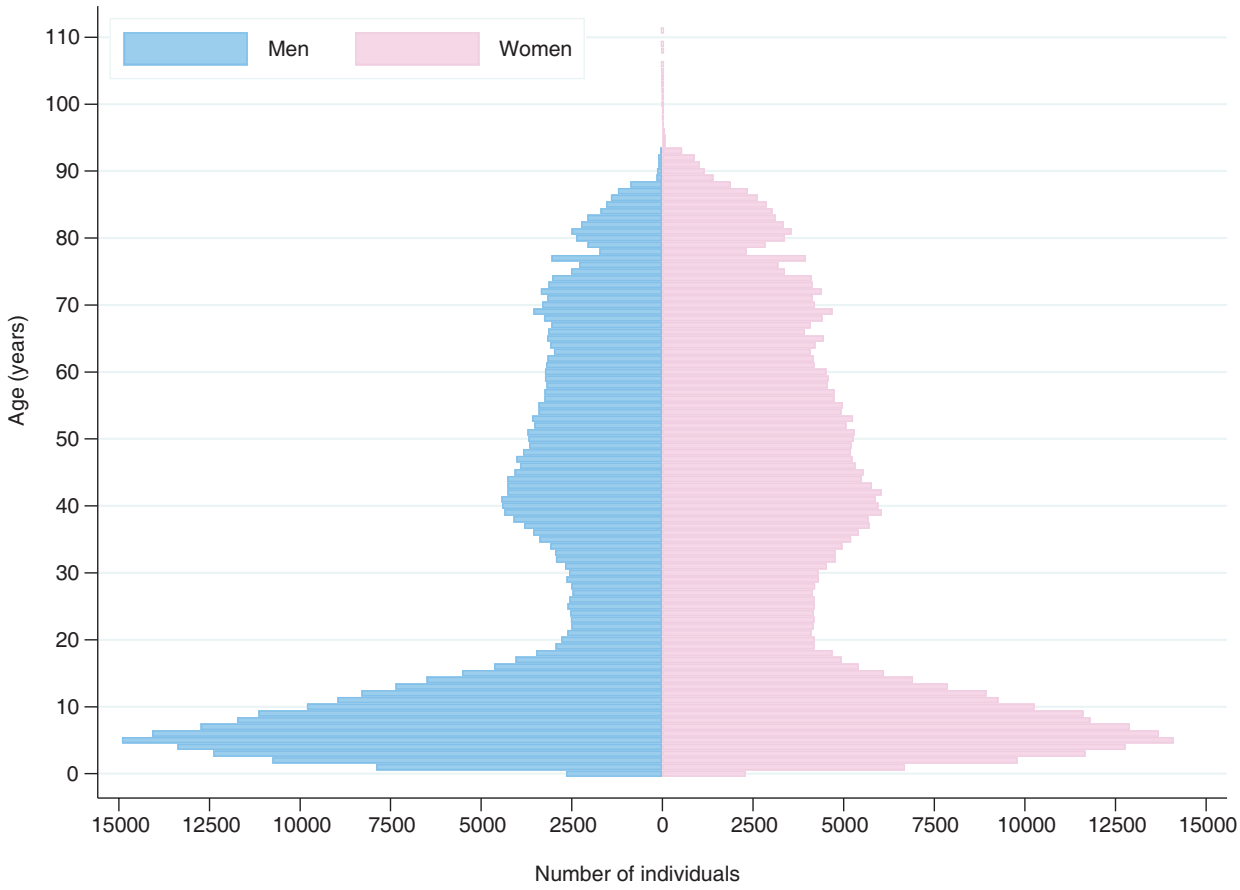

Figure 1 Population pyramid for individuals with atopic dermatitis in Catalonia in 2017.

The average value for serum tIgE among those individuals was 102.0 KU/L (CI: 99–105.4). Serum tIgE values were significantly higher ($p < 0.05$) in severe than non-severe AD (155.5 KU/L vs 101.9 KU/L, respectively). About 61.4% of non-severe AD vs 74.0% of severe AD were above the threshold amongst those with available laboratory information.

Comorbidities

Allergic rhinitis (15.0%), asthma (13.5%) and acute bronchitis (13.2%) were the most frequent respiratory/allergic comorbidities. Being overweight (11.1%) and having anxiety (6.5%) are the most prevalent factors in the adolescent AD population among the non-respiratory comorbidities (Table 3). A higher proportion of all comorbidities was reported in severe vs non-severe AD patients, with a significant difference for co-existing asthma in patients with severe AD (21.2%) vs non-severe AD (13.5%), for co-existing allergic rhinitis in patients with severe AD (19.1%) vs non-severe AD (15%) and for co-existing food allergy in patients with severe AD (2.6%) vs non-severe AD (1.1%).

Although not the most frequent of comorbidities, nasal polyposis and chronic obstructive pulmonary disease (COPD) should be highlighted among the rest of the respiratory and allergic comorbidities for having the strongest associations with severe AD (ORs: 3.88, 3.33, respectively, $p < 0.0001$) and hypertension among the systemic ones (OR 4.51, $p < 0.0001$) (Table 3).

Discussion

To date and to our best knowledge, this is the first retrospective population-based epidemiological study analysed in more considerable adolescent AD patients (76,665) than in previous studies and with richer patient information for Spain. The main findings were: 1) the overall diagnosed prevalence of AD for the adolescent population of Catalonia was 16.9%; 2) AD is higher among the non-severe (16.7%) than the severe (0.2%) population; 3) in general, drug prescription was more elevated in severe than non-severe AD patients for all treatments, with emphasis for systemic corticosteroids and non-steroidal systemic immunosuppressants; and 4) a higher proportion of adolescents with severe AD is found with respiratory and allergic comorbidities mainly for asthma (21.2%), as well as overweight (11.1%) and anxiety (6.5%).

Our study is based on medical records from the Catalan health care system at the primary, hospital or emergency care level, which allowed the identification of a cohort of 76,665 adolescents (16.9% of the studied adolescent population aged 12–17 years) with AD over the 2013–2017 study period in Catalonia. The prevalence is in line with the Spanish adolescent prevalence (19.8%).[7] This is, however, the first Catalan study reporting the overall diagnosed prevalence for a whole adolescent cohort in this case. Another study[9] calculated the prevalence for adolescents between 13 and 18 years old (6.4%) with much lower results

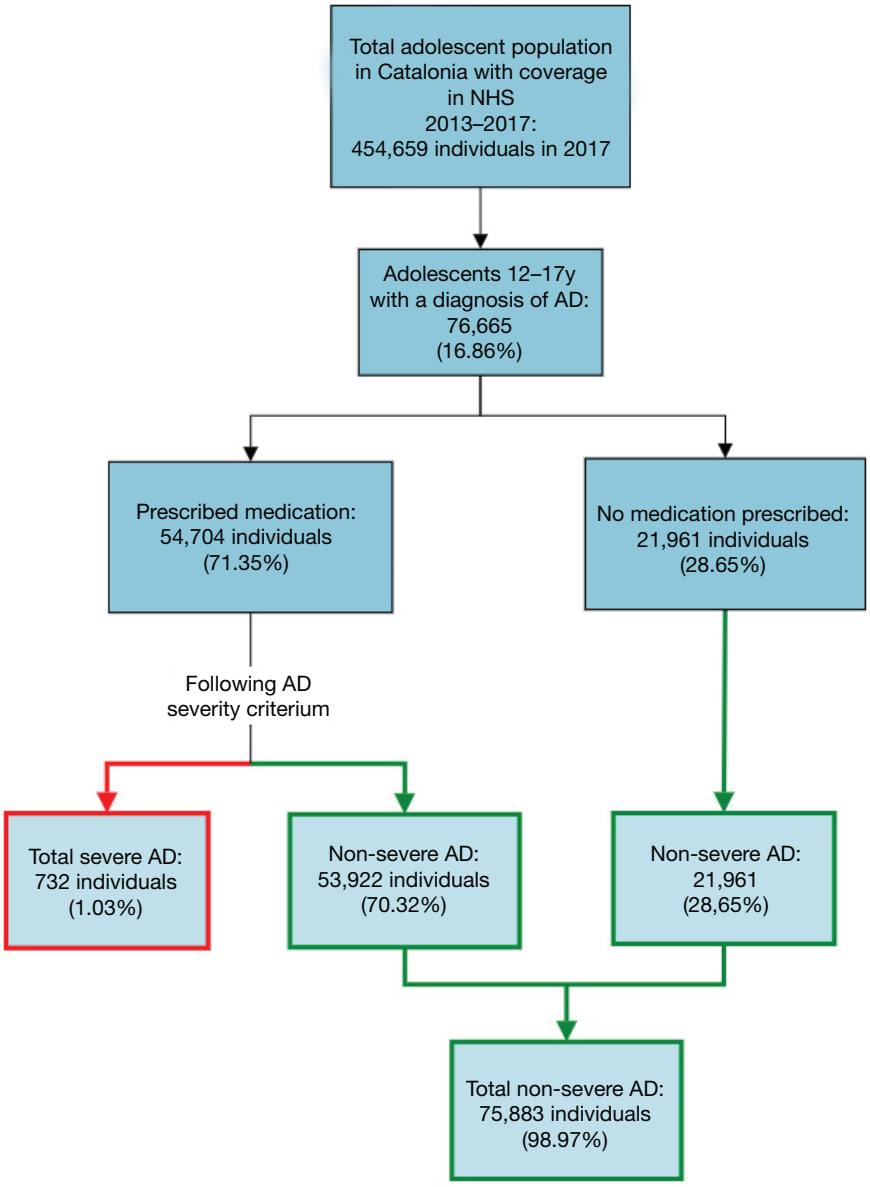

Figure 2 Flowchart classification of the adolescent atopic dermatitis cohort, overall and by disease severity according to prescribed medication. Among all individuals from the study population who received a diagnosis of atopic dermatitis (76,665 individuals), the type and amount of medication received for the treatment of atopic dermatitis (AD) could be retrieved for 71.4% of the cases (54,704 individuals). Based on this severity criterion, 782 individuals were classified as with severe AD and 75,883 individuals as non-severe. Patients with no information on drug consumption over the study period were assumed to be non-severe AD (21,961 individuals). This assumption relies on the fact that severe medication for AD might be expensive, most likely retrieved from pharmacies. Therefore, those diagnosed at the NHS but without medication might be individuals with mild AD who might not need treatment or decided not to take the prescribed medication, perhaps because of mild symptoms. NHS: National Health Service.

than in the present study. This could be explained because different methodologies for both studies have been used. The previous studies rely on a smaller population (6,841 patients with 13–18 years) from seven Spanish regions in Spain, whereas the current study is based on the overall Catalan population.

Moreover, the inclusion criterion for the existing literature studies was more restrictive than the present study, including only those attending a specialist visit. This leads to a much lower prevalence than this study and a possible sample bias. Yet, to date, the present population-based study is the first to analyse the prevalence of AD in the adolescent population using a much larger-scale database in Catalonia (Spain).

The overall diagnosed prevalence of severe AD was 0.17%. The prevalence found in this study tends to be smaller than the ones found in the existing literature[7] (3.3% for the 13–18 age group) given the small sample of patients

Table 1 Sociodemographic characteristics of adolescent atopic dermatitis cohorts.

Sociodemographic characteristics	Overall N = 76,665	Non-severe N = 75,883 (98.98)	Severe N = 782 (1.02%)
Gender, N (%)			
Males	36,423 (47.5)	36,085 (47.6)	338 (43.2)
Females	40,242 (52.5)	39,798 (52.4)	444 (56.8)
Chi2 (5.87; $p = 0.015$)			
Age, years, N (%)			
[12–17]	76,665 (100%)	75,883 (98.98)	782 (1.02)
Chi2 (147.09; $p < 0.0001$)		3,737 (4.9)	51 (6.5)
Income, Euros, N (%)			
Exempted	3,788 (4.9)	3,737 (4.9)	51 (6.5)
<18,000	46,366 (60.5)	45,891 (60.5)	475 (60.7)
18,000–100,000	25,920 (33.8)	25,668 (33.8)	252 (32.2)
>100,000	591 (0.8)	587 (0.8)	4 (0.5)
Chi2 (91.97 $p < 0.0001$)			

N: Number of individuals. Number of individuals in each population (adolescents). The proportion of individuals over the total population in each population is in parentheses. P-values are for Pearson's chi-square test of independence between categorical variables. Data on income were only available for 2017.

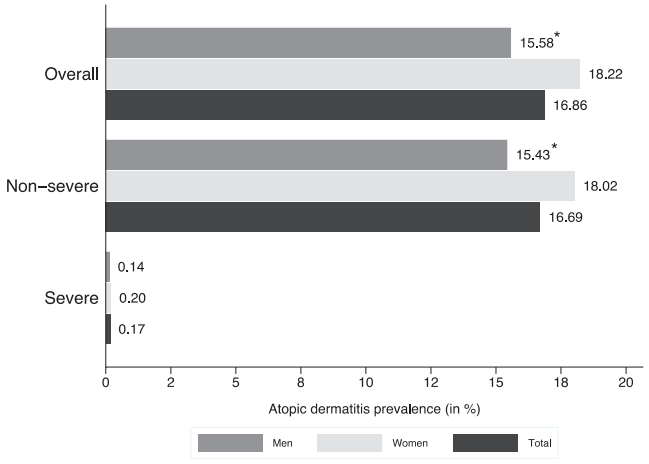

Figure 3 Prevalence of atopic dermatitis (AD) in the Catalan adolescent population (2013–2017). Statistical analysis of the difference in prevalence by gender within each group (overall, non-severe, severe): *$p < 0.001$.

with AD compared to ours and given the different prescribed treatment used to classify individuals into severe and non-severe. Besides, previous literature is based on two self-reported questionnaires: IGA scale (the 5-point investigator's global assessment) and POEM (patient oriented eczema measure). Specifically, in the Spanish study, immunoglobulin treatment was used as a severity criterion, with 18% of the adolescent population with AD being treated. In line with earlier studies,[15] we found gender differences, with females having a higher overall prevalence (18.2%) than males (15.6%), and by severity groups.

Regarding the use of drugs, the European and World Guidelines on the Treatment of AD recommend limiting the use of systemic steroids, and the fact that around 50% of adolescents with severe AD have been treated with systemic steroids is cause for concern, especially with the risk of relapse, HPA axis suppression, risk of glaucoma and other numerous side effects.[16] This study finds more treatment prescriptions for patients with severe AD than

Table 2 AD adolescent cohort according to disease severity by prescribed treatment.

Performed treatment N during last two years (%)	Overall cohort N = 76,665	Cohort by severity Non-severe N = 75,883 (98.97%)	Severe N = 782 (1.03%)	P-value
Drugs				
Topical CS	37,899 (49.5)	37,303 (49.2)	596 (76.2)	<0.0001
Systemic CS	13,516 (17.6)	13,127 (17.3)	389 (49.7)	<0.0001
Antihistamines	33,583 (43.8)	33,011 (43.5)	572 (73.1)	<0.0001
Immunosuppressants	3,352 (4.4)	2,997 (4.0)	355 (45.4)	<0.0001
No drugs/Non severe	21,961 (28.7)	21,961 (29.0)	-	-

CS: Corticosteroids; AD: atopic dermatitis. In parentheses, the proportion of individuals over the total adolescent population in each phenotype (total, non-severe and severe). P-values are for the test of differences in means between the severity degrees for each treatment under study at a 95% confidence level of significance (Null hypothesis (Ho): No statistically significant differences between severity degrees. Reject Ho if p-value < 0.05). A total of 76,416 individuals had no drug information and were assumed to have non-severe AD. Drugs are not mutually exclusive, as one individual can simultaneously prescribe more than one group of medications.

Table 3 Comorbidities of the adolescent cohort (12–17 years old).

	Total population	Population by disease severity				
		Non-severe	Severe		Logit regression Pr (severe)	
AD related comorbidities	N = 76,665	N = 75,883	N = 782	P-value	Odds ratio (95% CI)	P-value
Respiratory & allergy, N (%)						
Asthma	10,382 (13.5)	10,216 (13.5)	166 (21.2)	p < 0.0001	1.59 (1.30–1.94)	<0.0001
Allergic rhinitis	11,516 (15.0)	11,367 (15.0)	149 (19.1)	0.0008	1.04 (0.85–1.28)	0.681
Acute bronchitis	10,105 (13.2)	9,977 (13.1)	128 (16.4)	0.004	1.04 (0.84–1.28)	0.702
Nasal Polyposis	90 (0.1)	85 (0.1)	5 (0.6)	p < 0.0001	3.88 (1.57–9.56)	0.003
COPD	134 (0.2)	128 (0.2)	6 (0.8)	p < 0.0001	3.33 (1.18–9.38)	0.023
Not specified allergy	4,056 (5.3)	3,978 (5.2)	78 (10.0)	p < 0.0001	1.76 (1.36–2.27)	<0.0001
Food allergy	817 (1.1)	797 (1.1)	20 (2.6)	p < 0.0001	1.80 (1.12–2.91)	0.016
Systemic & general, N (%)						
Hypertension	375 (0.5)	357 (0.5)	18 (2.3)	p < 0.0001	4.51 (2.66–7.64)	<0.0001
Overweight	8,508 (11.1)	8,413 (11.1)	95 (12.1)	0.17	1.003 (0.80–1.26)	0.975
Anxiety	5,008 (6.5)	4,940 (6.5)	68 (8.7)	0.007	1.20 (0.92–1.56)	0.183
Epilepsy	679 (0.9)	663 (0.9)	16 (2.0)	0.0002	1.98 (1.12–3.48)	0.018
Autism	402 (0.5)	397 (0.5)	5 (0.6)	0.33	0.87 (0.36–2.13)	0.765
ADHD	3,695 (4.8)	3,650 (4.8)	45 (5.8)	0.11	1.20 (0.88–1.65)	0.251

COPD: Chronic Obstructive Pulmonary Disease; ADHD: Attention Deficit Hyperactivity Disorder; AD: atopic dermatitis. Number of adolescent AD patients in each phenotype (total, non-severe and severe) by related comorbidities. The proportion of individuals over the total adolescent population in each phenotype is in parentheses. P-values are for the test of differences in means between severity degrees (non-severe vs severe) for each comorbidity under study at a 95% confidence level of significance (Null hypothesis (Ho): No statistically significant differences between severity degrees. Reject Ho if p-value < 0.005). Logistical regression analysis for the probability of severe. The model includes sociodemographic characteristics as control variables.

non-severe ones, especially regarding topical and systemic corticosteroids and immunosuppressants.

The current trend in treating chronic diseases is to consider the preferences and opinions of the patient as well as involve the patient in the choice of medical treatment to ensure greater adherence.[17] Adolescent patients with AD may have low adherence to the treatment prescribed by their doctor and overuse of topical and/or systemic corticosteroids.[18] The average individual reported serum tIgE values were higher for severe AD than for non-severe, as similarly found in the previous literature.[19–21]

Respiratory and allergy comorbidities were the most frequent, especially for those with severe AD. In line with earlier studies,[9,22] asthma (13.5%) and allergic rhinitis (15.0%) were the most prevalent in adolescents. And, it is also reported that 92% of AD adolescent patients have ≥ 1 concurrent allergic condition. Among the AD severe group, asthma was the most prevalent. Among systemic comorbidities, overweight and anxiety were found in higher proportions, as suggested by the existing literature.[9,23–25]

This study also has some limitations. First, the retrospective nature of the research and the fact that the severity of treatment is retrieved from prescribed medication instead of medical diagnosis. Prescribed medication is understood as prescribed and purchased by the individuals. However, information on whether taken or not is not available. Second, we cannot determine whether some drugs, such as systemic corticosteroids, were prescribed to treat AD or other concomitant diseases. Therefore, use of corticoid intake as a severity criterion was not used. On the other hand, the prevalence of severe AD patients could also be underestimated by assuming patients with no drug information present a non-severe AD which might or might not always be the case. And third, the lack of inclusion of individuals diagnosed and treated outside of the statutory NHS, in private hospitals or medical centres, could underestimate the prevalence and disease severity results.

In summary, this paper aims to contribute to the literature by providing new evidence by using a more significant number of AD patients than in previous studies, including richer information on most patients diagnosed with AD from the general adolescent population of Catalonia. Our findings show an overall prevalence of 16.9%, more prevalent for females than males overall and regardless of the severity. The prevalence of severe AD was 0.17% and tended to increase for females slightly. Finally, the most frequent comorbidities were acute bronchitis, asthma and allergic rhinitis, among the respiratory and allergies.

Authorship Contribution

TM and IS-C performed the database analysis. IS-C, PR, AV and TM analysed the results and wrote the manuscript. JM and RM-C collaborated in the development and correction of the manuscript.

Conflict of Interest

All the authors received specific funding for developing this work from the International University of Catalonia (UIC)

Real-World Evidence Chair. There are no patents, products in development or marketed products to declare. The authors of this manuscript have no relevant financial or other relationships to disclose.

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Supplementary

Study design

Coverage in the NHS in Catalonia is universal. According to *Idescat* (the Statistical Institute of Catalonia), in 2017, there were 454,659 adolescent (12–17 years) residents in Catalonia. Numbers provided by *AQuAS* indicated that 99.1% of them were covered in the NHS. Therefore, the database virtually encompasses the entire population of Catalonia that uses public health resources. Medical records include a patient identifier, registry date in the primary, hospital or A&E care, medical diagnosis, medical procedures and registries of drug consumption regarding the type of drug and defined daily dosage (DDD). The DDD is a measure developed by the World Health Organization that indicates the assumed average daily maintenance dose for a drug used for its main indication in adults (World Health Organization, 2020). It does not necessarily reflect the prescribed daily dose, which may vary according to the patient's characteristics, but it allows international drug consumption comparisons.

Treatment codes available in the database were (ATC codes are given in parentheses):

1. Topical corticosteroids:
   a. Low potency: fluocinonide acetonide 0.0025%/0.00625–0.01% (D07AC08); hydrocortisone aceponate (D07AC16); methylprednisolone aceponate 0.25% (D07AC14).
   b. Medium potency: prednicarbate 0.25% (D07AC18); betamethasone valerate 0.025% (D07AC01); lobetasone butyrate 0.05% (D07AB01); desoximetasone 0.05% (D07AC03); fluocinonide acetonide 0.00625–0.01% (D07AC08); fluocortin butile 0.75% (D07AB04); hydrocortisone aceponate 0.1% (D07AC16); hydrocortisone butyrate 0.1% (D07AA02).
   c. High potency: betamethasone dipropionate 0.05% (D07AC01); beclomethasone dipropionate 0.025% (D07AC15); betamethasone valerate 0.1% (D07AC01); diflorasone diacetate 0.05% (D07AC10); hydrocortisone butyrate 0.1% (D07AA02); methylprednisolone aceponate 0.1% (D07AC14); mometasone furoate 0.1% (D07AC13); fluticasone propionate 0.1% (D07AC17); fluocinonide (D07AC08; D07CC05) (with antibiotics).
   d. Ultra-high potency: clobetasol propionate 0.05% (D07AD01); hydrocortisone 17 butyrate (D07AB02); methylprednisolone aceponate (D07AC14); mometasone furoate (D07AC13); fluticasone propionate (D07AC17).
2. Antihistamines: dexchlorpheniramine (R06AB02), cetirizine (R06AE07), levocetirizine (R06AE09), loratadine (R06AX13), desloratadine (R06AX27), rupatadine (R06AX28), ebastine (R06AX22), fexofenadine (R06AX26), bilastine (R06AX29).
3. Immunosuppressant agents: Tacrolimus (D11AH01; L04AD02), pimecrolimus (D11AH02), ciclosporin (L04AD01), azathioprine (L04AX01), cyclophosphamide (L01AA01), methotrexate (L04AX03; L01BA01), alitretinoin (D11AH04), mycophenolic acid (L04AA06), interferon alpha-2a (L03AB04), interferon alpha-2b (L03AB05).
4. Corticosteroids for systemic use: Prednisone (H02AB07), methylprednisolone (H02AB04), hydrocortisone (H02AB09), triamcinolone (H02AB08), dexamethasone (H02AB02), deflazacort (H02AB13), prednisolone (H02AB06).

Comorbidities

The following comorbidities were studied (main ICD-9-CM): acute bronchitis (466.X), allergic rhinitis (AR) (477.X), asthma (493.0X. 493.1X, 493.2X, 493.8X, 493.9X), food allergy (693.1), not a specified allergy (995.3) CRS with nasal polyps (CRSwNP) (471, 471.0, 471.9), chronic obstructive pulmonary disease (COPD) (491.21, 491.0). Also, hypertension, overweight, anxiety, epilepsy autism and attention deficit hyperactivity disorder (ADHD) were studied.