Prevalence of Atopic Dermatitis in the adult population of Catalonia (Spain): a retrospective, large-scale population-based study

Short title: Epidemiology of Atopic Dermatitis

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ABSTRACT

Introduction: Studies on the prevalence of Atopic Dermatitis (AD) for the adult cohort in general-based populations are scarce worldwide. We performed a retrospective population-based observational cohort study of 537,098 adult patients diagnosed with AD in Catalonia (Spain), a larger population than in previous studies.

Objectives: To study the prevalence of AD generally by age, gender, disease severity, multi-morbidities, and serum total Immunoglobin E (tIgE) and undergo appropriate medical treatment (AMT) for the Catalan population.

Methods: Adult individuals (≥18 years old) diagnosed with AD by medical records at different health care levels (primary, hospital, emergency) from the Catalan Health System (CHS) were included. Statistical analyses were conducted to evaluate socio-demographic characteristics, prevalence, multi-morbidities, serum tIgE and AMT.

Results: The overall diagnosed AD prevalence in the adult Catalan population was 8.7%, being higher for the non-severe (8.5%) than for the severe (0.2%) populations and females (10.1%) than males (7.3%). Topical corticosteroids were the most prescribed drug (66.5%), and the use of all prescribed treatments was higher in severe AD patients, especially systemic corticosteroids (63.8%) and immunosuppressant agents (60.7%). More than half (52.2%) of severe AD patients reported serum tIgE ≥ 100 KU/L, and higher values were observed for those with multi-morbidities. Acute bronchitis (13.7%), allergic rhinitis (12.1%), and asthma (8.6%) were the most frequent comorbid respiratory diseases.

Conclusions: Our study provides new and robust evidence of AD's prevalence and related characteristics in adults using a large-scale population-based study and a more significant cohort of individuals.

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Key words: Atopic Dermatitis. Epidemiological study. Population-based. Prevalence. Severity. Multi-morbidities. Total serum IgE.

RESUMEN

Introducción: Existen pocos estudios de prevalencia de Dermatitis Atópica (AD) con cohortes de población adulta a nivel mundial. Realizamos un estudio poblacional de cohortes retrospectivo observacional con 537.098 pacientes adultos diagnosticados de AD en Cataluña (España), una población mayor que en estudios previos.

Objetivos: Estudiar la prevalencia de la AD por edad, sexo, gravedad de la enfermedad, comorbilidades, inmunoglobina E total sérica (tIgE) y con un uso adecuado del tratamiento médico (ATM) en la población catalana.

Métodos: Se incluyeron personas adultas (≥ 18 años) diagnosticadas de AD por historia clínica en los diferentes niveles asistenciales (primaria, hospitalario, urgencias) del Sistema Catalán de la Salud. Se realizaron análisis estadísticos para evaluar características sociodemográficas, prevalencia, comorbilidades, tIgE sérica y ATM.

Resultados: La prevalencia global de AD diagnosticada en la población adulta catalana fue del 8,7%, siendo mayor la AD no grave (8,5%) que la AD grave (0,2%) y en el sexo femenino (10,1%) con respecto al masculino (7,3%). Los corticoides tópicos fueron el fármaco más prescrito (66,5%), y el uso de todos los tratamientos prescritos fue mayor en pacientes con AD grave, especialmente corticoides sistémicos (63,8%) e inmunosupresores (60,7%). Más de la mitad (52,2%) de los pacientes con AD grave presentaron tIgE sérica ≥ 100 KU/L, y se observaron valores más altos en aquellos con múltiples comorbilidades. La bronquitis aguda (13,7%), la rinitis alérgica (12,1%) y el asma (8,6%) fueron las enfermedades respiratorias concomitantes más frecuentes.

Conclusiones: Nuestro estudio proporciona evidencia nueva y sólida de la prevalencia de la AD y las características relacionadas en adultos utilizando un estudio poblacional a

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gran escala y una cohorte de individuos más significativa que los estudios previamente publicados.

Palabras clave: Dermatitis atópica. Estudio epidemiológico. Poblacional. Prevalencia. Gravedad. Comorbilidades. IgE sérica total.

INTRODUCTION

Atopic dermatitis (AD) and its related states (atopic eczema, eczema, neurodermatitis) is a non-contagious, pruritic, inflammatory skin condition with defects in the epidermal barrier. It is chronically relapsing, often occurring in families with atopic diseases: atopic dermatitis, bronchial asthma and/or allergic rhino-conjunctivitis [1]. According to the European Academy of Allergy and Clinical Immunology, Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis or eczema/dermatitis [2].

The pathogenesis of AD is multifactorial [3]. The genetic component plays a significant influence, but also the skin microbiome and environmental factors. AD usually starts during childhood, the most common cutaneous disease in children, with a high impact on an individual's quality of life. Infants with AD may develop the *atopic march,* which relates to the joint development of atopic disorders, including food allergy, allergic rhinitis, and asthma [3,4,5]. Severe cases may persist over time and are more often during adulthood.

The epidemiology of AD reports estimated global prevalence of about 2% to 8% in adults [1]. In Europe, 4.4% of the population is estimated to have AD. For the USA, numbers vary between 4.9% [6] and 10.2% [7]. Evidence of the estimated prevalence for Spanish adults is scarce, and results vary between 1.9% [8,9] to 7.2% [6], with vast differences among geographical regions. The prevalence estimates for severe AD range between and 0.07% [9] and 0.09% [10].

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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, multi-morbidities, total serum IgE levels, and undergo medical treatments of an AD cohort of adults from Catalonia (Spain). To our knowledge, this is the first population-based epidemiological study analysed in a more significant population of AD patients and with richer patient information than the samples used by previous literature. Hence, this allows for more robust prevalence results for the overall adult population and by age groups, as well as data on disease severity, multi-morbidities, medical treatments, and biomarkers for Spain.

MATERIALS AND METHODS

Study population

All residents in Catalonia - the second largest populated region in Spain - with coverage in the state 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: a) Patients age ≥ 18 years, and b) 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 different for everyone in the dataset). Exclusion criteria: a) subjects transferred to other regions in Spain, and b) permanently institutionalised patients (i.e., patients were living in nursing homes, psychiatrists, or other care facilities). Overall, there were 537,098 patients with AD diagnosis over the 2013-2017 study period constituting the population under study.

Data obtained was 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*.

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Study design

The database was provided by AQuAS 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 - Atopic dermatitis and related states - Other atopic dermatitis and associated conditions: AD, eczema, neurodermatitis; 692.9 - contact dermatitis and another eczema, unknown cause. Including the second code might overestimate the prevalence because of including irritant or allergic contact dermatitis and other non-atopic dermatoses. Notwithstanding, not considering that code would not pick up a consistent number of AD registered in that way.

The type of prescribed AD therapies (topical corticosteroids, antihistamines, topical and systemic 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.

Outcomes

1. Demographic characteristics

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

2. Epidemiology

The overall diagnosed AD prevalence in the general adult population was calculated based on all individuals from the study population who received a diagnosis of AD over

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the total adult population in Catalonia (6,155,980 residents in 2017). Since the database encompasses the entire population of Catalonia, prevalence results do not represent estimated values. Instead, data should be interpreted as the diagnosed prevalence in Catalonia over 2013-2017.

3. Disease severity

Since symptoms data was not available in the dataset, neither was the SCORAD scale [1,11], disease severity classification (non-severe, severe) was based on drug prescription following the existing literature [9,10].

Everyone's drug prescription over the last two years was considered to capture the most updated degree of severity. Individuals were classified as presenting severe AD disease when: 1) prescription of immunosuppressant agents (ciclosporin, azathioprine, cyclophosphamide, methotrexate, alitretinoin, mycophenolic acid, interferon alpha-2a, interferon alpha-2b) of at least one time over the last two years; or 2) one or more hospitalisations/emergencies over the last two years with AD as a first diagnostic. Patients were considered non-severe in all other situations.

4. Total serum IgE biomarker

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

5. Multi-morbidities

AD multi-morbidities, including respiratory/allergy and systemic/general, were also analysed and found in the supplementary material.

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.

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Statistical analyses were conducted using the statistical package Stata 16. A descriptive study reported frequencies and proportions of individuals in the overall population and by disease severity for confounders, multi-morbidities, treatment characteristics, and biomarkers. Pearson's chi-square test of independence between categorical variables where reported, as well as mean differences by disease severity. Odds Ratio (OR) with a 95% Confidence Interval (CI) and p-values were reported for the multivariate logistic regression on the probability of having severe atopic dermatitis against multi-morbidities and confounders. The overall prevalence of atopic dermatitis was reported, as well as the prevalence by disease severity, all analysed by gender and age groups. A p-value < 0.05 was considered statistically significant.

RESULTS

Descriptive characteristics

Even though the population under study is adults, it is worth noticing that most AD cases concentrate during childhood and until 15 years old (**Figure 1 online supplementary figures**). After that, the population shrinks with fewer AD cases for adults, but enough to be the object of study.

537,098 adults out of 6,155,980 Catalan residents in 2017 had a diagnosis of AD. Among them, 2.4% (12,860 individuals) were classified as presenting severe AD, and 97.6% (524,238 individuals) as having non-severe AD (**Figure 2 online supplementary figures**).

More women than men had a diagnosis of AD (1.46:1) for both non-severe and severe (1.52:1) disease. The diagnosis of AD is more frequent (65%) in young adults (18-59) than in the ≥60 years old population, and the same is valid among the non-severe and severe subgroups. More than half (70%) of the AD adult cohort had annual incomes <18,000€ (**Table 1**).

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AD prevalence

The diagnosed prevalence of AD was 8.7%, higher in the non-severe vs severe group (8.5% vs 0.2%) (**Figure 3 online supplementary figures**). By gender, the overall prevalence was higher for females than males (10.1% vs 7.3%, p<0.0001) and in the severity groups. The prevalence is highest for women between 18-29 years old (11.2%). The prevalence increases over time for both genders. Specifically for men, being highest (9.6%) for those 60 years old and above (**Figure 4A online supplementary figures**). Differences in prevalence between males and females are statistically significant (p<0.0001) from 30 years old onwards. A similar pattern for both genders is observed for non-severe AD (**Figure 4B online supplementary figures**). However, the prevalence for females with severe AD slightly increases with age.

Prescribed treatment

Within the 2013-2017 study period, topical corticosteroids were the most prescribed drugs in the population (66.5%) and each severity group (66.3% for non-severe and 77.9% for severe). It followed antihistamines (53.2%) and systemic corticosteroids (24.9%). All medications were more prescribed in severe than non-severe AD patients; this difference is especially significant for systemic corticosteroids (63.8% vs 24%, respectively) and immunosuppressant agents (60.7% vs 4.5%). 16% of individuals had no prescription for any AD treatment and were considered mild (**Table 2**).

Total serum IgE

During the last 2-year period (2016-2017), there were 14,841 individuals with available information on serum total IgE (tIgE) (**Table 3**). From those with available data, 6,320 (42.6%) reported serum tIgE values ≥100 KU/L. This proportion was higher in the severe than the non-severe (52.2% vs 42.1%, p<0.0001) groups, and for those AD patients with multi-morbidities (asthma: 60.8%; nasal polyps (NP): 45.9%; and both asthma and NP: 60.7%) than those without (38.4%, p<0.0001) (**Figure 5 online supplementary figures**). Serum tIgE values were significantly higher (p<0.05) in severe than non-severe AD (110 KU/L vs 72.3 KU/L, respectively). Concerning multi-morbidities, patients with asthma,

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NP, or both, showed higher levels of serum tIgE than those without multi-morbidities (**Table 3**).

Multi-morbidities

Acute bronchitis (13.7%), allergic rhinitis (12.1%), and asthma (8.6%) were the most frequent respiratory/allergic multi-morbidities. Hypertension (28.2%), anxiety (20.9%), and overweight (19.2%) were the most prevalent among the non-respiratory multi-morbidities (**Table 4**). A higher proportion of all multi-morbidities was reported in severe vs non-severe AD patients, with a significant difference between those having severe AD and asthma (15%) for non-severe (8.4%) and those with allergies and severe AD (9.2%) vs non-severe AD (4.8) and acute bronchitis.

In the same line, asthma, not specified allergies, and food allergy should be highlighted among the rest of respiratory and allergic multi-morbidities for having the strongest associations with severe AD (ORs: 1.83, 1.95, 1.54, respectively), and rheumatoid arthritis among the systemic ones (OR 22.63, p<0.0001) (**Table 4**).

DISCUSSION

This is the first retrospective population-based epidemiological study analysed in a more significant population of adult AD patients. With higher patient information for Spain, with a total sample of 6,1 million residents, this study should be considered the main strength. The main findings were: 1st) the overall diagnosed prevalence of AD for the adult population of Catalonia was 8.7%, being higher for the non-severe (8.5%) than for the severe (0.2%) population; 2nd) AD was more frequent among females than males for the overall AD population and irrespectively of the disease severity and age range; 3rd) AD prevalence decreased during the lifespan for females and increased for males for the comprehensive, and by severity groups, except for females with severe AD where it slightly increases through age; 4th) in general, drug prescription was higher in severe than non-severe AD patients for all treatments, with emphasis for systemic corticosteroids and immunosuppressants; 5th) serum tIgE values were higher for severe

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than for non-severe (52.2% vs. 42.1%, p<0.0001) populations, and for those AD patients with multi-morbidities (asthma: 60.8%; NP: 45.9%; and asthma and NP: 60.7%); 6th) A higher proportion of individuals with severe AD is found with respiratory and allergic multi-morbidities, as well as systemic, specially anxiety (20.9%), and hypertension (28.2%). There was also a strong association between rheumatoid arthritis and the probability of severe AD (OR 22.63, p<0.0001).

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 537,098 adults with a diagnosis of AD established by medical records covered by all the NHS, an 8.7% of the studied population in Catalonia. This prevalence is very similar to recent reported data [6] (2018) for Spanish adults up to 65 years old (7.2%), which used questionnaire data for the diagnoses of AD on a sample of 9,924 individuals.

Prevalence rates in this study are higher than those in the existing literature for Spain [9,10]. One reason to overestimate in the present study is the inclusion of the ICD9-CM code 692.9. However, in our case, not accounting for that code would considerably underestimate the overall prevalence to 1.61% (99,062 individuals). This could be explained because different methodologies for both studies have been used. The previous studies rely on a smaller population from seven Spanish regions in Spain, whereas the current study is based on the Catalan adult population.

Moreover, the inclusion criteria for the existing literature studies were more restrictive than for the present study. Recent literature for the Spanish case [10] used medical register data for adults above 18 years old; however, including only those individuals that met all the following inclusion criteria: prescription of any medication for AD with a minimum of 2 drugs during the follow-up period, ≥2 health records including one dermatology visit (38,475 individuals) which leads to a much-restricted population and therefore a lower prevalence result (1.9%) and a possible sample bias. Another difference in this result is the age group classification compared to previous studies [10], which is above 18 years (not including 18 years of patients in this group, which could increase the prevalence result). Yet, to date, the present population-based study is the

doi: 10.18176/jiaci.0899

first analysing the prevalence of AD in the adult population using a much larger-scale database and including all public medical registers of individuals with a diagnosis of AD over the 2013-2017 study period in Catalonia (Spain) constituting a much bigger sample of individuals with severe AD.

On the other hand, the prevalence of severe AD (0.21%) was more significant than the ones found in the existing literature, that is, 0.08% [8] and 0.07% [10] For the same reasons explained above and, given the fact that due to the disease nature, the AD severity is retrieved from the prescribed medication instead of medical diagnosis. In these studies, related to Spain [8,9,10,11], the medicine used was directly associated with AD treatment. In contrast, it was impossible in this study to distinguish whether the drugs were explicitly prescribed to treat AD or other concomitant diseases.

In line with earlier studies [6,7], we found significant gender differences, with females having a higher overall prevalence (10.1%) than males (7.3%) and also by severity groups and over the lifespan, where the prevalence tends to decrease for both genders, except for females with severe AD.

Following the European Guidelines on Treatment for Atopic Dermatitis [1] concerning medication usage, this study finds higher treatment prescriptions for severe AD patients than for non-severe, especially concerning the use of systemic corticosteroids (63.8% vs 24%, respectively) and immunosuppressant agents (60.7% vs 4.5%).

Higher values for serum tIgE were found for severe AD and individuals presenting with multi-morbidities (asthma and/or NP). Despite the lack of consensus on the use of serum tIgE for the diagnoses of AD [3] and the fact that it might be age-dependent with tIgE levels decreasing with age [12,13], 42.6% of individuals reported serum tIgE values ≥ 100 KU/L, where this proportion was higher for severe AD (52.2%), as similarly found in previous literature [14], and for those with multi-morbidities [15,16].

Respiratory and allergy multi-morbidities were the most frequent, especially for those with severe AD compared to those with non-severe AD. In line with earlier studies [8,10,17,18], the most prevalent multi-morbidities for the total adult AD population

doi: 10.18176/jiaci.0899

were acute bronchitis (13.7%), allergic rhinitis (12.1%), and asthma (8.6%) and among the severe adult population: acute bronchitis (18.5%), allergic rhinitis (11.6%), and asthma (15%). However, there are differences in the % of multi-morbidities observed in the severe AD population from other studies [10], which are higher: allergic rhinitis (22.9%) and asthma (20.8%).

Moreover, a recent study [18] showed that 82% of patients with moderate-to-severe AD have ≥1 atopic comorbidity, including allergic rhinitis (63%), asthma (54%), allergic conjunctivitis (44%), food allergy (40%), chronic rhinosinusitis (14%), atopic keratoconjunctivitis (8%) and nasal polyps (5%).

It can be concluded that there is a high correlation between atopic dermatitis and type-2 diseases which is even more frequent in severe AD patients, and that the proportion of comorbidities in this study could be reduced due to the restrictive inclusion criteria.

Among systemic multi-morbidities, the most frequent were: hypertension (28.2%), anxiety (20.9%), and overweight (19.2%), which were found in lower proportions as suggested as well by the existing literature [10,20,21]. Moreover, although the frequency of patients with rheumatoid arthritis (0.8%) was lower than other systemic multi-morbidities, it had one of the strongest associations with severe AD (OR 22.63) in line with previous studies [22].

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. Note that ruling out oral corticosteroids as a criterion of severity could have introduced bias between the severe and non-severe clusters. Biological treatment was not considered, given the low implementation during the period and because the reasons for this treatment were unknown. Second, we must find a way to disentangle whether some drugs, such as OCS, were prescribed to treat AD or other concomitant diseases specifically. Therefore, the use of OCS intake as a severity criterion was not used. On the

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other hand, the prevalence for 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 state NHS in private hospitals or medical centres could underestimate the prevalence and disease severity results.

In summary, there is more evidence regarding the prevalence of AD in children, but less is known about the prevalence in adults. This paper aims to contribute to the literature by providing new evidence on that by using a more significant number of AD patients than previous studies, including richer information on most of the patients diagnosed with AD from the general adult population of Catalonia. Our findings show an overall prevalence of 8.72%, more prevalent for females than males overall and irrespectively of the severity and age range. The prevalence for severe AD is 0.21% and tends to increase slightly across age groups for females and decrease for males. Values for serum tIgE ≥ 100 were found in 42.6% of individuals, in whom this proportion was higher for severe AD and those with multi-morbidities. Finally, the most frequent multi-morbidities were acute bronchitis, allergic rhinitis, and asthma among the respiratory and allergic ones, and hypertension, anxiety, and obesity among the systemic and nonallergic ones.

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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TABLES

Table 1. Sociodemographic characteristics of the adult Atopic Dermatitis cohort.

	Overall Cohort	**Cohort by severity**	
Socio-demographic characteristics	**N = 537,098** (100%)	**Non-severe N = 524,238** (97.6%)	**Severe N =12,860** (2.4%)
Gender, N (%)			
Males	217,999 (40.6)	212,895 (40.6)	5,104 (39.7)
Females	319,099 (59.4)	311,343 (59.4)	7,756 (60.3)
Chi^2 (4.42; p=0.036)			
Age, years, N (%)			
18-59	349,335 (65)	341,503 (65.1)	7,832 (60.9)
≥ 60	187,763 (35)	182,735 (34.9)	5,028 (39.1)
Chi^2 (99.28; p<0.0001)			
Income, Euros, N (%)			
Exempted	26,071 (4.9)	25,359 (4.8)	712 (5.5)
< 18,000	380,118 (70.8)	370,852 (70.7)	9,266 (72.1)
18,000-100,000	129,273 (24.1)	126,420 (24.1)	2,853 (22.2)
> 100,000	1,636 (0.3)	1,607 (0.3)	29 (0.2)
Chi^2 (37.83; p<0.0001)			

Abbreviations: N – Number of individuals.

Note: Number of individuals in each phenotype (total, non-severe, and severe). The proportion of individuals over the total adult population in each phenotype is in parenthesis. P-values are for Pearson's chi-square test of independence between categorical variables. Data on income was only available for 2017.

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Table 2. Adult Atopic Dermatitis cohort according to disease severity by prescribed treatment.

	Overall cohort	Cohort by severity		
Performed treatment N (%)	**N = 537,098** (100%)	**Non-severe N = 524,238** (97.6%)	**Severe N =12,860** (2.4%)	**P-value**
Drugs				
Topical CS	357,362 (66.5)	347,349 (66.3)	10,013 (77.9)	<0.0001
Systemic CS	133,766 (24.9)	125,565 (24.0)	8,201 (63.8)	<0.0001
Antihistamines	285,591 (53.2)	276,215 (52.7)	9,376 (72.9)	<0.0001
Immunosuppressants	31,650 (5.9)	23,849 (4.5)	7,801 (60.7)	<0.0001
No drugs	87,533 (16.3)	87,533 (16.7)	-	-

Abbreviations: CS – Corticosteroids.
Note: In parenthesis, the proportion of individuals over the total adult 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). 87,533 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.

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Table 3. Total IgE values for the Atopic Dermatitis adult cohort over the 2016-2017 period.

Biomarkers - Median and mean values (95% CI)	Total Population	By disease severity		By multi-morbidities			
		Non-severe	Severe	AD alone	AD + Asthma	AD + NP	AD + Asthma + NP
Serum total IgE	**N = 14,841**	**N = 14,172**	**N = 669**	**N = 11,887**	**N = 2,472**	**N = 268**	**N = 214**
Median KU/L	73.4 (71.09 - 76.1)	72.3 (70 – 74.9)	110* (94.8- 132.4)	62.8 (60.2 - 64.8)	153* (143 - 166)	86* (62.15 - 106)	132.6* (112 - 171.9)
Mean KU/L	275.4 (0.1 – 1,513.1)	259.5 (0.1 – 1,405.6)	582.1 (0.1 – 2,903.1)	227.8 (0.1 – 1,286.9)	474.9* (0.8 – 2,246.9)	270.0* (0.2 – 1,327.1)	441.4* (2.2 – 2,039.4)

Abbreviations: Immunoglobulin E; AD – Atopic Dermatitis; NP – Nasal Polyposis.
Notes: for IgE, median and average values are calculated and reported across the maximum value reported for everyone with available information on the biomarker between 2016-2017. 95% Confidence Intervals were reported in parenthesis for the median value and the test of statistically significant differences in means across severity degrees and among multimorbidity phenotypes (*, P-value < 0.05). Median values were preferred above average as the Kernel distribution for each biomarker was very asymmetric with extremely high skewness and Kurtosis.

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Table 4. Multi-morbidities of the adult Atopic Dermatitis cohort.

	Total Population	Population by disease severity				
AD related multi-morbidities	**N = 537,098**	**Non-severe** **N = 524,238** (97.61%)	**Severe** **N =12,860** (2.39%)	**P-value**	**Logit regression Pr (severe)** **Odds Ratio (95% CI)**	**P-value**
Respiratory & allergy, N (%)						
Asthma	45,934 (8.6)	44,009 (8.4)	1,925 (15.0)	p<0.0001	1.83 (1.74 - 1.94)	p<0.0001
Allergic rhinitis	64,993 (12.1)	63,498 (12.1)	1,495 (11.6)	0.047	0.85 (0.80 - 0.90)	p<0.0001
Acute bronchitis	73,608 (13.7)	71,225 (13.6)	2,383 (18.5)	p<0.0001	1.12 (1.07 - 1.19)	p<0.0001
Nasal Polyposis	4,849 (0.9)	4,689 (0.9)	160 (1.2)	p<0.0001	1.16 (0.98 - 1.37)	0.085
COPD	8,318 (1.5)	7,985 (1.5)	333 (2.6)	p<0.0001	1.04 (0.92 - 1.18)	0.536
Not specified allergy	26,295 (4.9)	25,113 (4.8)	1,182 (9.2)	p<0.0001	1.95 (1.83 - 2.08)	p<0.0001
Food allergy	1,747 (0.3)	1,661 (0.3)	86 (0.7)	p<0.0001	1.54 (1.22 - 1.93)	p<0.0001
Systemic & general, N (%)						
Hypertension	151,486 (28.2)	147,021 (28.0)	4,465 (34.7)	p<0.0001	1.16 (1.1 - 1.22)	p<0.0001
Overweight	103,080 (19.2)	100,375 (19.1)	2,705 (21.0)	p<0.0001	0.93 (0.89 - 0.98)	0.005
Dyslipidaemia	57,399 (10.7)	55,467 (10.6)	1,932 (15.0)	p<0.0001	1.18 (1.12 - 1.25)	p<0.0001
Diabetes	58,871 (11.0)	57,027 (10.9)	1,844 (14.3)	p<0.0001	1.15 (1.08 – 1.22)	p<0.0001
Ischemic heart disease	21,087 (3.9)	20,384 (3.9)	703 (5.5)	p<0.0001	1.06 (0.97 - 1.16)	0.191
Alcohol related disease	16,721 (3.1)	16,105 (3.1)	616 (4.8)	p<0.0001	1.36 (1.24 - 1.49)	p<0.0001
Tobacco related diseases	75,756 (14.1)	73,577 (14.0)	2,179 (16.9)	p<0.0001	1.16 (1.10 - 1.22)	p<0.0001
IB disease	6,943 (1.3)	6,758 (1.3)	185 (1.4)	0.07	0.98 (0.84 - 1.14)	0.775
Rheumatoid arthritis	4,418 (0.8)	2,913 (0.6)	1,505 (11.7)	p<0.0001	22.63 (21.12 - 24.24)	p<0.0001
Heart/liver/renal failure	6,108 (1.1)	5,839 (1.1)	269 (2.1)	p<0.0001	1.58 (1.38 - 1.80)	p<0.0001
Anxiety	112,084 (20.9)	109,207 (20.8)	2,877 (22.4)	p<0.0001	1 (0.95 - 1.04)	0.944
Depression	25,679 (4.8)	24,829 (4.7)	850 (6.6)	p<0.0001	1.12 (1.03 - 1.21)	0.005

Abbreviations: COPD – Chronic Obstructive Pulmonary Disease; IB – Inflammatory Bowel. Alcohol-related diseases include alcohol induced-mental disorders, alcohol dependence and abuse, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of the liver, the excessive blood level of alcohol, toxic (acute) effect of alcohol, alcoholic gastritis with or without mention of haemorrhage, fetal alcohol syndrome. Tobacco-related diseases include Chronic pharyngitis, uncomplicated chronic bronchitis, and leukoplakia of oral mucosa, including the tongue.

Note: Number of AD individuals in each phenotype (total, non-severe, and severe) by related multimorbidities. The proportion of individuals over the total adult population in each phenotype is in parenthesis.

P-values are for the test of differences in means between severity degrees (non-severe vs severe) for each multimorbidity 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.

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