Prevalence of Chronic Rhinosinusitis with Nasal Polyps in Catalonia (Spain): a retrospective, large-scale population-based study*

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Abstract

Background: Studies on the prevalence of chronic rhinosinusitis (CRS) with nasal polyps (NP) in general-based populations are scarce in Europe and worldwide. We performed a retrospective population-based observational cohort study of 30,189 adult patients diagnosed with NP in Catalonia (Spain).

Methodology: Adult individuals (≥18 years old) with a diagnosis of NP established by medical records at different health care levels (primary, hospital, and emergency) from the Catalan Health System (CHS) were included. Socio-demographic characteristics, prevalence, overall and by age and gender, disease severity, multi-morbidities, and biomarkers of type-2 inflammation were evaluated, together with appropriate medical treatment (AMT) and Endoscopic Sinus Surgery (ESS).

Results: In general population and severity sub-populations, the overall diagnosed NP prevalence was 0.49% and higher for males than females (0.60% vs 0.39%, p<0.0016). The prevalence for the severe NP population was 0.12%. The NP prevalence increased with age, the highest being at ≥ 60 years old for both gender and severity groups. Asthma (40.1%), acute rhinosinusitis (41.1%), and allergic rhinitis (32.1%) were among the most frequent comorbid respiratory diseases. ESS was performed in 15.4% of NP patients. Type 2 inflammation was present in 83.8% of the NP population and was more frequent in severe than non-severe (87.1% vs 82.7%, p<0.0001) patients and in those with respiratory multi-morbidities (91%).

Conclusions: This is the first large-scale population-based NP epidemiology study conducted in Spain, including severity based on undergoing medical and surgical treatment and type 2 inflammation. Although the prevalence data are lower than in previous European studies, the large NP cohort studied represents an essential strength of the results.

Key words: nasal polyps, epidemiology, population-based, prevalence, type-2 inflammation

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease affecting the mucosa of the nasal cavities and paranasal sinuses clinically diagnosed by assessing symptoms (nasal congestion/obstruction/blockage, nasal discharge/postnasal drip, reduction/loss of smell, and/or facial pain/pressure for more than 12 weeks) [1]. CRS has two main phenotypes, with (CRSwNP) or without (CRSsNP) nasal polyps. Its differential characteristics can advise a specific approach in terms of diagnosis (CT scan for sinonasal occupation, and nasal endoscopy for nasal polyps) and therapeutic management [1-4]. CRSwNP patients usually present with multi-morbidities, especially asthma [5,6] and NSAID-

exacerbated respiratory disease (N-ERD) [7].

Based on EPOS 2012 [3] and EPOS 2020 [1], treatment for CRSwNP should be administered according to severity of disease. In EPOS 2020 [1], the recommended tool to assess disease severity was the score of Visual Analogue Scale (VAS) for total sinonasal symptoms. The appropriate medical treatment (AMT) for CRSwNP is constituted by saline nasal lavage and intranasal corticosteroids (INCS), either in spray or drops, and short courses of oral corticosteroids (OCS) in severe cases or exacerbations. Endoscopy sinus surgery (ESS) is only recommended when the AMT has failed in patients with severe CRswNP [1]. In EPOS 2020 [1], treatment of severe patients is addressed depending on the presence of type 2 inflammation (based on high levels of blood eosinophils or serum total IgE), which is present in 85% of CRSwNP patients in Europe and other western countries (US and Australia) [8].

CRSwNP has a highly significant adverse impact on patient's quality of life and daily social functioning due to severity of sinonasal symptoms, including the loss of smell [6,9,10]. The impact on health-related quality of life (HRQoL) is similar to other chronic conditions such as chronic obstructive pulmonary disease (COPD), asthma, and diabetes [11]. Moreover, the socio-economic burden of CRS and CRSwNP is higher than other chronic conditions such as acute asthma or chronic bronchitis [12]. The overall cost (direct and indirect) for CRS is estimated to be $30 billion per year in the US [13] and around $8,000 per patient/year [14]. The cost of CRSwNP in Europe is estimated to be > € 7,000 /patient/year for [15].

The epidemiology of CRS reports a prevalence of 11% in Europe [5] with some differences between countries worldwide [16]. In the case of CRSwNP, some prevalence in adult population-based studies include 2.1% in France [17], 2.7% in Sweden [18], 4.3% in Finland [19], and 0.5% in South Korea [20].

This 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, type 2 biomarkers, and undergone medical and surgical treatments of a NP cohort from Catalonia (Spain). To our knowledge, this is the first population-based epidemiological study providing data of disease severity and type 2 inflammation not only in Spain but also in Europe.

Materials and methods

Study population

The population under study encompasses all residents in Catalonia - the second largest populated region in Spain - with coverage in the statutory National Health Service (NHS) containing a diagnostic related to nasal polyposis (NP) at any of the care levels covered by the NHS (primary, hospital, and ambulance and emergency care), at any point in time from January 2013 until December 2017, being the follow-up period different for each individual in the dataset.

Inclusion and exclusion criteria

Patients from the study population requesting care regarding NP between January 2013 and December 2017 were included. Inclusion criteria were: a) age ≥ 18 years, and b) patients with a diagnosis of NP stablished by medical records at any care level covered by the NHS and following the diagnostic codes according with the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) [21] for NP. Exclusion criteria were: a) subjects transferred out to other regions in Spain, and b) permanently-institutionalized patients (i.e., patients living in nursing homes, psychiatrics, or other care facilities). Overall, there were 30,189 patients with a diagnosis of NP over the 2013-2017 study period and this cohort was used for the study.

Ethics

Data obtained was confidential, anonymous, and dissociated according to the Spanish Organic Law on Data Protection (Law 15/1999 of December 13). The study was classified by the Spanish Agency 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 CRSwNP. 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

Database description

The database was provided by the Agency for Health Quality and Assessment of Catalonia (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 individual-patient level of residents in Catalonia with coverage in the NHS. Coverage in the NHS in Catalonia is universal. According to Idescat (the Statistical Institute of Catalonia), in 2017 there were 7,555,830 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 makes use of public health resources. Medical records include a patient identifier, date of registry in primary, hospital or A&E care, medical diagnosis, medical procedures, and registries of drug consumption regarding type of drug and Define Daily Dosage (DDD).

Diagnostic codes

The current accepted term of chronic rhinosinusitis with nasal polyps (CRSwNP) was not found in the database. The diagnostic of NP was established using records grounded on medically certified diagnoses coded with the International Classification of

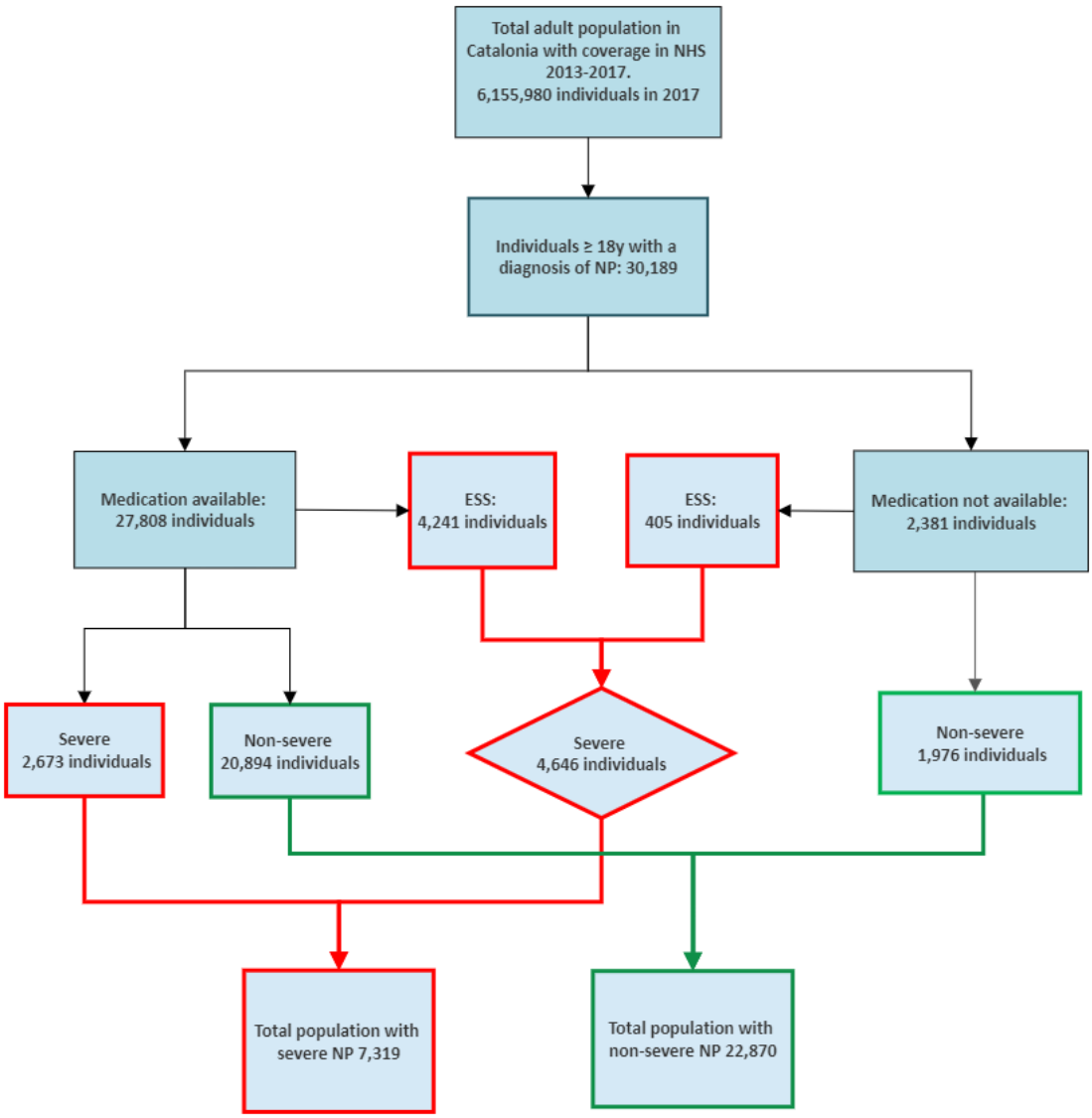

Figure 1. Flowchart classification of the nasal polyp cohort, overall and by disease severity according with prescribed medication and ESS. Among all individuals from the study population who received a diagnosis of NP (30,189 individuals), the type and amount of medication received for the treatment of NP could be retrieved for 92% of the cases (27,808 individuals). Based on consumption of OCS and ESS severity criterium, there were 7,319 individuals with severe NP (2,673 based on OCS-DDD only, and 4,241 individuals based on surgery and/or OCS-DDD, and 405 individuals based on ESS only with no information on drugs), and 20,894 individuals were classified as non-severe NP. Individuals with no information on drug consumption and no ESS performed over the study period were assumed to be non-severe NP (1,976 individuals). This assumption relies on the fact that severe medication for NP might be expensive, so most likely retrieved from pharmacies. Therefore, those diagnosed at the NHS but without medication might be individuals with mild NP who might not need treatment, or decided not to take the prescribed medication, perhaps because mild symptoms. Abbreviations: NP –Nasal Polyps; NHS – National Health Service; ESS: Endoscopic Sinus Surgery.

Diseases, 9th revision, Clinical Modification (ICD-9-CM) [21]. Individuals with the following ICD-9-CM codes as primary diagnostic were considered: 471 (nasal polyps), 471.0 (polyp of nasal cavity) and 471.9 (unspecified nasal polyp – nasal polyps NOS). Overall, there were 30,189 individuals in the database with CRSwNP as main diagnostic over the 2013-2017 period constituting the population under study. Concretely, there were 27,211 patients diagnosed in primary care, 6,114 patients in hospital care, and 419 patients in emergency care. Since individuals can be treated at different care levels over the study period, care level categories are not mutually exclusive.

Treatment codes

The type of prescribed therapies (active ingredients) available in the database for the period under study and indicated for the treatment of CRSwNP were (ATC codes are given in parentheses):

Table 1. Severity thresholds for oral corticosteroid intake (in milligrams).

Active Drug	Administration route	Mg in one DDD	Recommended doses (mg/day)	Threshold = (min_ dose*365.25) mg/year
Methylprednisolone	Oral	7.5	**4** - 16 – 40	1,461
Prednisolone	Oral	10	**5** - 10 - 15 - 20 – 30	1,826
Prednisone	Oral	10	**2.5** - 5 - 10 - 30 - 50	913
Trigon depot	IM	7.5	**40**	14,610
Deflazacort	Oral	15	**6** – 30	2,191

Abbreviations: Min dose - minimum recommended dose; IM - intramuscular. DDD – Define Daily Dose.
Note: Milligrams of each active drug in one DDD is in accordance with the ATC/DDD index 2021. See: https://www.whocc.no/atc_ddd_index/.
Recommended minimum doses are expressed in bold. Source: author's elaboration using the information from Vademecum and medical advisors.

1. Intranasal corticosteroids (INCS) - beclomethasone (R01AD01), budesonide (R01AD05), fluticasone propionate (R01AD08), mometasone furoate (R01AD09), triamcinolone (R01AD11), fluticasone furoate (R01AD12). 2. Oral Corticosteroids (OCS) - methylprednisolone (H02AB04), prednisolone (H02AB06), prednisone (H02AB07), trigon depot (H02AB08), deflazacort (H02AB13). 3. Antibiotics - erythromycin macrolide (J01FA01), doxycycline (J01AA02), roxithromycin macrolide (J01FA06). 4. Antihistamines (anti-H1) - diphenhydramine (R06AA02), doxylamine (R06AA09), doxylamine combinations (R06AA59), dexchlorpheniramine (R06AB02), mepyramine (R06AC01), thiethylperazine (R06AD03), mequitazine (R06AD07), cetirizine (R06AE07; R06AE57), levocetirizine (R06AE09), clocinizine (R06AE92), cyproheptadine (R06AX02), loratadine (R06AX13), ketotifen (R06AX17), ebastine (R06AX22), mizolastine (R06AX25), fexofenadine (R06AX26), desloratadine (R06AX27), rupatadine (R06AX28), bilastine (R06AX29). 5. Anti-leukotriene (anti-LTs) - montelukast (R03DC03).

Administered drug dosage

The Define Daily Dosage (DDD) for each individual's drug prescribed was used to approximate the actual doses of prescribed therapy for each individual under study. It is a measure developed by the World Health Organization that indicates the assumed average maintenance dose per day for a drug used for its main indication in adults [22]. It does not necessarily reflect the prescribed daily dose as this may vary according with patient's characteristics, but it allows international drug consumption comparisons.

Outcomes

Demographic characteristics

From the database information on socioeconomic and demographic characteristics were obtained: 1) gender; 2) adult age (continuous and by ranges : 18-29y, 30-39y, 40-49y, 50-59y, ≥60y); 3) four annual income levels were constructed and adjusted by household size (< € 18,000, € 18,000-€ 100,000, > € 100,000 Euros, and non-contributory or disability pensions termed as "exempted" [23]; and 4) six co-payment levels (exempted, 10%, 40%, 50%, and 60% of co-payment, and those excluded from co-payment). Information on those variables was only available for the year 2017 in the database.

Epidemiology

The overall diagnosed NP prevalence in the general adult population was calculated based on all individuals from the study population who received a diagnosis of NP (30,189 individuals) over the total adult population in Catalonia (6,155,980 residents in 2017). Therefore, the overall NP prevalence was calculated as the percentage of patients in the study population diagnosed with NP. 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 the years 2013-2017. Therefore, no confidence intervals are reported.

Prevalence results do not include individuals that are diagnosed and treated outside the statutory NHS. Medication for treatment of NP can be expensive and no reimbursement can be claimed for prescriptions done outside the NHS. It is therefore reasonable to expect that most individuals with CRSwNP will be treated in the NHS and thus included in this study.

Disease severity

Since information on VAS score or SNOT were not available in the dataset, the type and doses of prescribed medications for the treatment of NP as well as performed ESS were used to assess two degrees of disease severity (non-severe and severe). To capture the most updated degree of severity we looked at drug prescription over the last two years for each individual in the dataset.

Following this criterion and according with the treatment recommendation from EPOS 2020 consensus [1], individuals were classified as presenting severe CRSwNP disease when: 1) OCS

Table 2. Sociodemographic characteristics of the nasal polyp cohort.

Socio-demographic characteristics	Overall cohort N = 30,189 (100%)	Cohort by severity	
		Non-severe N = 22,870 (76%)	Severe N = 7,319 (24%)
Gender, N (%)			
Males	17,867 (59.2)	13,373 (58.5)	4,494 (61.4)
Females	12,322 (40.8)	9,497 (41.5)	2,825 (38.6)
Chi^2 (19.7; p<0.0001)			
Age, years, N (%)			
18-29	1,860 (6.2)	1,606 (7.0)	254 (3.5)
30-39	3,495 (11.6)	2,798 (12.2)	697 (9.5)
40-49	5,706 (18.9)	4,299 (18.8)	1,407 (19.2)
50-59	6,259 (20.7)	4,585 (20.0)	1,674 (22.9)
≥ 60	12,869 (42.6)	9,582 (41.9)	3,287 (44.9)
Chi^2 (182.4; p<0.0001)			
Income, Euros, N (%)			
Exempted	978 (3.2)	693 (3.0)	285 (3.9)
< 18,000	17,967 (59.5)	13,533 (59.2)	4,434 (60.6)
18,000-100,000	11,052 (36.6)	8,480 (37.1)	2,572 (35.1)
> 100,000	192 (0.6)	164 (0.7)	28 (0.4)
Chi^2 (30.1; p<0.0001)			
Co-payment, N (%)			
Exempted	978 (3.2)	693 (3.0)	285 (3.9)
10%	12,178 (40.3)	9,016 (39.4)	3,162 (43.2)
40%	10,161 (33.7)	7,885 (34.5)	2,276 (31.1)
50%	6,473 (21.4)	4,951 (21.6)	1,522 (20.8)
60%	192 (0.6)	164 (0.7)	28 (0.4)
Excluded	207 (0.7)	161 (0.7)	46 (0.6)
Chi^2 (63.3; p<0.0001)			

Abbreviations: N – Number of individuals.

Note: Overall number of individuals and in each severity degree (non-severe, and severe). Proportion of individuals over the total adult population in each phenotype in parenthesis. P-values are for the Pearson's chi-square test of independence between categorical variables. Data on income and co-payment was only available for 2017.

intake over the last two years was above the annual minimum dose calculated threshold for each OCS in any of the two years; or 2) need for CRSwNP surgery over the period with available information on ESS (2010-2017). Patients were considered of non-severe in all other situations.

The prescribed dose of OCS was needed to classify individuals into the severe CRSwNP criteria. Since this information was not directly available from the database, information on the number of DDDs consumed of each OCS by each patient was used. To approximate the actual "OCS dosing (mg)" prescribed to each individual we multiplied the average drug consumption in DDDs by the milligrams of OCS in one DDD stablished by the ATC/DDD index available at the World Health Organization [24].

Each OCS and its corresponding ATC code was associated with one DDD per route of administration. Hence, the ATC/DDD index establishes the equivalence between 1 DDD and the amount of OCS used. If a drug is administered using several routes, the DDDs provided by oral administration were preferred. To define a severity threshold for every OCS a minimum annual dose, multiplying the minimum daily recommended dosage (see www.vademecum.es) by 365.25 days, was calculated. The idea behind this approach relies on the fact that any patient taking the minimum dose of OCS over a whole year was presenting a severe NP. Therefore, all individuals prescribed with a particular OCS-DDD dose above its annual threshold were classified as severe NP. Table 1 shows the recommended doses for each

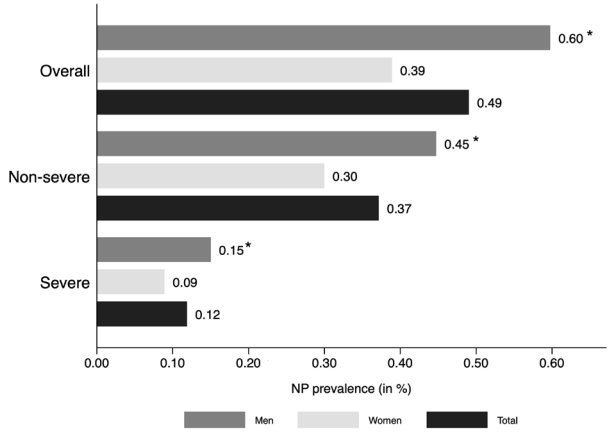

Figure 2. Prevalence of nasal polyps in the Catalan adult population (2013-2017).

Note: Statistical analysis on the difference in prevalence by gender within each phenotype (overall, non-severe, severe): * p<0.01.

OCS according with Vademecum and the calculated minimum annual doses used as threshold. The flowchart classification into severity categories according to the OCS-DDD and surgery criteria is provided (Figure 1). Overall, 24% of the NP population (7,319 individuals) was classified as having a severe NP while 76% as non-severe (22,870 individuals).

Biomarkers of type 2 inflammation

We studied two relevant biomarkers representing type 2 inflammation in clinical practice that contribute in assessing the diagnosis of the disease [1]: blood eosinophils and total immunoglobulin E (IgE) which data was also provided by the AQUAS dataset. The first multidisciplinary consensus document pointing out the use of total serum IgE and blood eosinophilia to determine type 2 inflammation in CRSwNP was presented by the EUFOREA group [30]. EPOS 2020 [1] was the following consensus reporting this guidance but adding cut points for both blood (≥250 eosinophils/μL) and nasal polyp tissue (≥10 eosinophils/High Power Field) eosinophils as well as for serum total IgE (≥100 KU/L).

Therefore, blood eosinophilia was defined as blood eosinophil counts ≥250 cells/μL, and ≥2.5% if measured in relative terms (1,25-28). For total serum IgE, values ≥100 KU/L were considered as high levels and a biomarker of type 2 inflammation [1]. Type 2 inflammation was considered when any of these two biomarkers exceed its respective cut-off point [1].

For these biomarkers, the maximum value reported for each individual with available information between the 2016-2017 study is taken. The median biomarker value (confidence interval) and proportion of individuals with type 2 inflammation were also calculated for each biomarker.

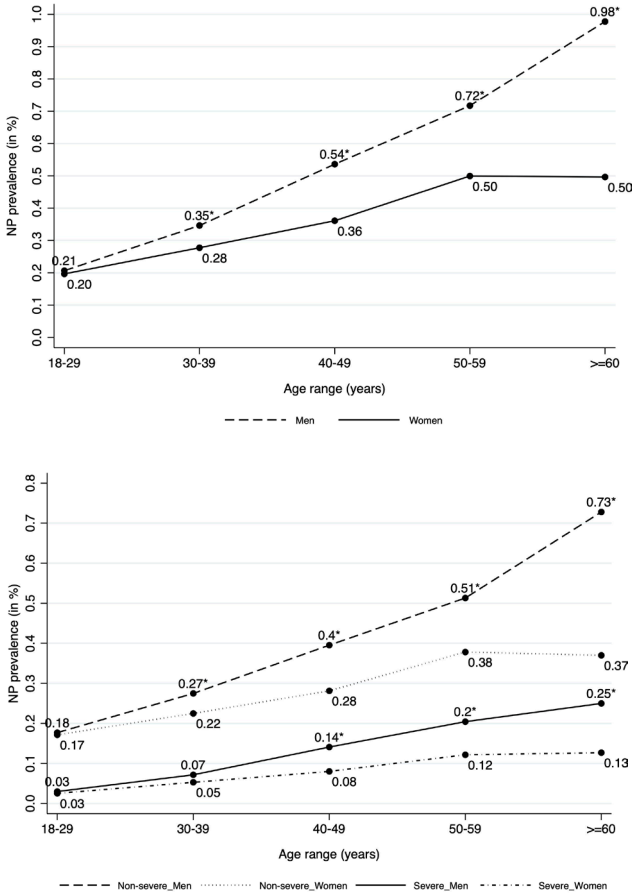

Figure 3. Prevalence of nasal polyps by gender and age groups (in % terms). A) Overall adult population; B) by disease severity. Statistical analysis: *, p<0.01.

Multi-morbidities

The main studied NP multi-morbidities were (main ICD-9-CM numbers): allergic rhinitis (AR) (ICD code number 477), asthma (493), acute bronchitis (466), atopic dermatitis (AD) (691.8, 692.9), acute rhinosinusitis (ARS) (460, 461, 465), aspirin/NSAID-exacerbated respiratory disease (V14.6), bronchiectasis (494), chronic obstructive pulmonary disease (COPD) (491). Also, hypertension, overweight, anxiety, dyslipidaemia, diabetes, depression, not specified allergy, ischemic heart disease, diseases due to alcohol consumption, epilepsy, organ failure (heart, liver, renal), stroke, Parkinson disease, dementia, and multiple sclerosis were analysed.

Statistical analysis

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

Statistical analyses were conducted using the statistical package Stata 16. Descriptive analysis was conducted reporting frequen-

Table 3. Nasal polyp cohort according to disease severity by prescribed treatment.

Performed treatment N (%)	Overall cohort N = 30,189 (100%)	Cohort by severity Non-severe N = 22,870 (76%)	Severe N = 7,319 (24%)	P-value
Drugs				
Intranasal CS	25,582 (84.7)	19,290 (84.3)	6,292 (86.0)	0.0004
Systemic CS	16,103 (53.3)	10,389 (45.4)	5,714 (78.1)	<0.0001
Antihistamines	19,708 (65.3)	14,556 (63.6)	5,152 (70.4)	<0.0001
Antileukotrienes	3,926 (13.0)	2,367 (10.3)	1,559 (21.3)	<0.0001
Antibiotics	1,247 (4.1)	818 (3.6)	429 (5.9)	<0.0001
No drugs	2,381 (7.9)	1,976 (8.6)	405 (5.5)	<0.0001
Endoscopic Sinus Surgery	4,646 (15.4)	0 (0)	4,646 (63.5%)	<0.0001

Abbreviations: CS – Corticosteroids.

Note: Proportion of individuals over the total adult population in each phenotype (total, mild-to-moderate, and severe) in parenthesis. P-values are for the test of differences in means between severity degrees for each multi-morbidity under study at 95% confidence level of significance (Null hypothesis (Ho): No statistically significant differences between severity degrees. Reject Ho if p-value < 0.05). Individuals under ESS are directly classified as having severe CRSwNP. Biologics were not yet indicated for CRSwNP but for others inflammatory diseases such as asthma. 2,381 individuals had no information of drugs and where assumed to have a mild-to-moderate CRSwNP except for those who appear to have had an ESS (405 individuals) who were classified as severe. Drugs are not mutually exclusive as one individual can be prescribed with more than one group of drugs at the same time as well as ESS.

cies and proportion 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 95% Confidence Interval (CI) and p-values where reported for the multivariate logistic regression on the probability of having a severe NP against multi-morbidities and confounders. The overall prevalence of NP was reported, as well as the prevalence by disease severity (non-severe, severe), all of them analysed by gender and by age groups. A p-value < 0.05 was considered statistically significant.

Results

Demographic characteristics (Table 2)

More men than women had a diagnosis of NP (1.45:1), for both non-severe and severe (1.61:1) disease. The diagnosis of NP, both non-severe and severe, increased with age the highest number of diagnosed patients (42.6%) being at ≥60 years old group. More than half of the NP cohort had annual incomes < €18,000 while 40.3% of individuals have a co-payment level of 10%.

Nasal polyp prevalence (Figures 2 and 3)

The overall prevalence of NP was of 0.49%, being higher the non-severe vs severe group (0.37% vs 0.12%) (Figure 2). By gender, the overall prevalence was higher in males than females (0.60% vs 0.39%, p<0.0016) and also in the severity groups. The prevalence of NP increased with age for both male and female, the highest being over 60 years in male (Figure 3A). The differences on NP prevalence between male and female were growing with age, the largest being in the over ≥ 60-year group. This was also true in non-severe and severe phenotypes (Figure 3B).

Performed treatments (Table 3)

Intranasal corticosteroids were the most prescribed drug (85%) followed by antihistamines (65.3%), systemic corticosteroids (53.3%), and antileukotrienes (13%). The prescription of antibiotics and biologics was <5% in NP patients. All medications were more prescribed in severe than non-severe NP patients, this difference being especially significant for systemic corticosteroids (78.1% vs 45.4%, respectively). One out of 12 (7,9%) individuals had no information on drug intake and were considered non-severe except for those undergoing ESS (N= 405) who were classified as severe.

Regarding ESS, 15.4% of the overall NP cohort underwent surgery, all of them being severe, since this was a severity inclusion criterion, representing 63.5% of them undergoing surgery. Among them, almost all NP patients (95.3%) had one surgery, 4.3% had two, and the rest had ≥3 surgeries (up to 6 surgeries).

Type 2 biomarkers (Figure 4 and Table 4)

During the last 2-year period (2016-2017), there were 19,441 individuals with available information on blood eosinophils,

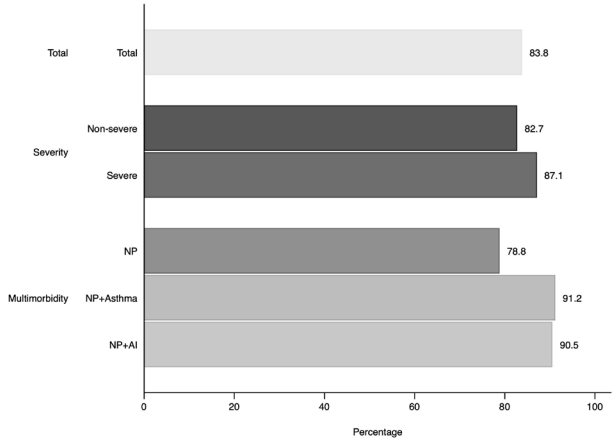

Figure 4. Proportion of individuals with type 2 inflammation in the nasal polyp cohort over the 2016-2017 period.

Abbreviations: AI - aspirin/NSAID intolerance; NP – Nasal polyposis.

Note: Proportion of individuals with type 2 inflammation in the total studied population, in the severity sub-populations, and by multimorbidity. Type 2 inflammation was considered when either blood eosinophil counts ≥250 cells/µL, or when eosinophils were ≥2.5%, or when IgE ≥100 KU/L. Differences between severe and non-severe sub-populations, and between individuals with multi-morbidities (asthma, and/or AI) and those without are statistically significant with p-value < 0.0001.

both absolute and relative counts, while only 1,258 individuals had information on serum total IgE.

From those with available information on biomarkers, 13,375 (68.8%) NP patients had a blood absolute eosinophil count ≥250 cell/µL, while 16,178 (83.2%) individuals had a blood relative eosinophil count ≥2.5%. More than a half (N=697, 55.4%) NP reported serum total IgE values ≥100 KU/L. Thus, 83.8% of patients achieved criteria of type 2 inflammation. This proportion was higher in the severe than the non-severe (87.1% vs. 82.7%, p<0.0001) NP sub-population, and for those NP patients with multi-morbidities (asthma: 91.2%; aspirin/NSAID intolerance: 90.5%) than for those without (78.8%, p<0.0001).

All biomarkers values were significantly higher (p<0.05) in severe than non-severe CRSwNP: absolute eosinophil counts (400 vs. 310 cell/µL), relative eosinophil counts (5.4% vs. 4.7%), and serum total IgE (140 KU/L vs. 108 KU/L). Concerning to multimorbidities, NP patients with asthma and aspirin/NSAID intolerance showed higher levels of type 2 biomarkers (both absolute and relative eosinophil counts, and total IgE) than those without multi-morbidities.

Multi-morbidities (Table 5)

The most frequent respiratory and allergy multi-morbidities in the NP cohort were acute rhinosinusitis (41.1%), asthma (40.1%), and allergic rhinitis (32.1%), while aspirin/NSAID intolerance was reported in 4.3% of the cases. Chronic rhinosinusitis (intrinsic for CRSwNP) was identified only in 11.1% of the patients. Among systemic general multi-morbidities the most frequent were hypertension (33.1%) and overweight (20.5%), while anxiety (18.1%) was the most frequent among psychiatric and neurological multi-morbidities.

Table 4. Type 2 biomarker values for the nasal polyp cohort over the 2016-2017 period.

Biomarkers - Median values (95% CI)	Total Population	By disease severity		By multimorbidities		
		Non-severe	Severe	NP alone	NP + Asthma	NP + AI
Blood eosinophils	N = 19,441	N = 14,555	N = 4,886	N = 11,546	N = 6,979	N = 916
Absolute value, Eos/µl	340 (330 - 350)	310 (300 - 320)	400* (400 - 400)	300 (300 - 300)	400* (400 - 430)	465* (410 - 500)
Relative value, %	4.8 (4.8 - 4.9)	4.7 (4.6 - 4.7)	5.4* (5.2 - 5.5)	4.1 (4.1 - 4.2)	6.8* (6 - 6.2)	6.1* (5.8 - 6.4)
Serum total IgE	N = 1,258	N = 875	N = 383	N = 501	N = 628	N = 129
KU/L	120 (108.3 - 128)	108 (97.7 - 122.7)	140* (124.6 - 157.4)	88.4 (64.9 - 99.6)	137* (125 - 150)	128* (114 - 196)

Abbreviations: IgE - Immunoglobulin E; AI - aspirin/NSAID intolerance.

Notes: for each biomarker, median values are calculated and reported across the maximum value reported for each individual with available information on the biomarker between the 2016-2017 period. 95% Confidence Intervals reported in parenthesis for the median value and for the test of statistically significance differences in means across severity degrees and among multimorbidity phenotypes (*, P-value < 0.05). Median values were preferred above average values as the Kernel distribution for each biomarker was very asymmetric with extremely high skewness and Kurtosis. For instance, for eosinophils measured in absolute value, skewness was 9.22 and Kurtosis 201.38.

Table 5. Multimorbidities of the nasal polyp cohort.

NP related multimorbidities	Total Population N = 30,189	Population by disease severity				
		Non-severe N = 22,870 (76)	Severe N = 7,319 (24)	P-value	Logit regression Pr (severe)	
					Odds Ratio (95% CI)	P-value
Respiratory & allergy, N (%)						
Acute rhinosinusitis	12,404 (41.1)	9,296 (40.6)	3,108 (42.5)	0.0030	0.99 (0.94 - 1.05)	0.7374
Asthma	12,119 (40.1)	8,270 (36.2)	3,849 (52.6)	p<0.0001	1.67 (1.58 - 1.77)	p<0.0001
Allergic rhinitis	9,679 (32.1)	7,138 (31.2)	2,541 (34.7)	p<0.0001	1.06 (1.00 - 1.13)	0.0395
Acute bronchitis	5,373 (17.8)	3,502 (15.3)	1,871 (25.6)	p<0.0001	1.50 (1.40 - 1.61)	p<0.0001
Atopic dermatitis	5,079 (16.8)	3,838 (16.8)	1,241 (17.0)	0.3645	1.04 (0.97 - 1.12)	0.2679
Aspirin/NSAID intolerance	1,296 (4.3)	648 (2.8)	648 (8.9)	p<0.0001	2.06 (1.83 - 2.33)	p<0.0001
Bronchiectasis	887 (2.9)	512 (2.2)	375 (5.1)	p<0.0001	1.58 (1.37 - 1.83)	p<0.0001
COPD	849 (2.8)	414 (1.8)	435 (5.9)	p<0.0001	2.14 (1.84 - 2.48)	p<0.0001
Not specified allergy	1,496 (5.0)	1,032 (4.5)	464 (6.3)	p<0.0001	1.32 (1.17 - 1.48)	p<0.0001
Food sensitivity	144 (0.5)	86 (0.4)	58 (0.8)	p<0.0001	1.84 (1.30 - 2.61)	0.0006
Systemic & general, N (%)						
Hypertension	9,991 (33.1)	7,314 (32.0)	2,677 (36.6)	p<0.0001	0.98 (0.91 - 1.05)	0.5704
Overweight	6,198 (20.5)	4,451 (19.5)	1,747 (23.9)	p<0.0001	1.13 (1.05 - 1.21)	0.0007
Dyslipidaemia	3,381 (11.2)	2,163 (9.5)	1,218 (16.6)	p<0.0001	1.56 (1.43 - 1.70)	p<0.0001
Diabetes	3,269 (10.8)	2,328 (10.2)	941 (12.9)	p<0.0001	1.06 (0.97 - 1.16)	0.1974
Ischemic heart	1,378 (4.6)	963 (4.2)	415 (5.7)	p<0.0001	1.01 (0.89 - 1.16)	0.8337
Alcohol related disease	926 (3.1)	632 (2.8)	294 (4.0)	p<0.0001	1.16 (1.00 - 1.36)	0.0544
Heart/liver/renal failure	320 (1.1)	229 (1.0)	91 (1.2)	0.0392	1.02 (0.79 - 1.32)	0.8666
Psychiatric & neurologic, N (%)						
Anxiety	5,461 (18.1)	4,073 (17.8)	1,388 (19.0)	0.0127	0.99 (0.92 - 1.06)	0.7535
Depression	1,497 (5.0)	1,042 (4.6)	455 (6.2)	p<0.0001	1.09 (0.96 - 1.23)	0.1792
Stroke	549 (1.8)	399 (1.7)	150 (2.0)	0.0447	0.96 (0.78 - 1.18)	0.7096
Epilepsy	329 (1.1)	232 (1.0)	97 (1.3)	0.0129	1.16 (0.90 - 1.50)	0.2507
Parkinson disease	178 (0.6)	140 (0.6)	38 (0.5)	0.1830	0.66 (0.44 - 1.00)	0.0504
Dementia	102 (0.3)	68 (0.3)	34 (0.5)	0.0160	0.90 (0.55 - 1.46)	0.6572
Multiple sclerosis	39 (0.1)	26 (0.1)	13 (0.2)	0.0925	1.27 (0.61 - 2.63)	0.5190

Abbreviations: COPD – Chronic Obstructive Pulmonary Disease; NSAID, non-steroidal anti-inflammatory drug. 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 liver, excessive blood level of alcohol, toxic (acute) effect of alcohol, alcoholic gastritis with or without mention of haemorrhage, fetal alcohol syndrome.

Note: Number of CRSwNP individuals in each phenotype (total, mild-to-moderate, and severe) by related multimorbidities. Proportion of individuals over the total adult population in each phenotype in parenthesis.

P-values are for the test of differences in means between severity degrees (mild-to-moderate vs severe) for each multimorbidity under study at 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. Model includes sociodemographic characteristics as control variables.

A higher proportion of almost all respiratory and allergy multimorbidities, except atopic dermatitis, was reported in severe vs non-severe NP patients. Among them, the association of chronic rhinosinusitis (OR 2.30), aspirin/NSAID intolerance (OR 2.06), and

asthma (OR 1.67), but also of COPD (OR 2.14), food sensitivity (OR 1.84), and bronchiectasis (OR 1.58) in severe NP patients should be highlighted. All systemic general (OR 1.46 for dyslipidaemia) and most of psychiatric neurological multi-morbidities were also reported more frequently in severe than in non-severe NP patients.

Discussion

The main findings of this retrospective population-based epidemiologic study were:

1st) the overall diagnosed prevalence of NP in the adult population in Catalonia was 0.49%, being 0.37% and 0.12%, respectively, for the non-severe and severe populations;

2nd) NP was more frequent among males than females (0.60% vs 0.39%) for the overall NP cohort and for both non-severe and severe subgroups;

3rd) NP prevalence increased during the lifespan and for both genders;

4th) the prevalence of NP for non-severe and severe NP sub-populations also increased with age and for both male and female with a maximal gender difference (male over female) in the ≥60 years group;

5th) Drug prescription of intranasal corticosteroids was the highest (85%) followed by antihistamines (65.3%) and systemic corticosteroids (53.3%). Surgery was performed in 15.4% of the overall NP cohort, most of them (95.3%) undergoing one surgery only.

6th) Among individuals with available information on the relevant biomarkers, the overall frequency of type 2 inflammation was of 83.8%, this percentage being higher among the severe (87.1%) than the non-severe (82.7%) NP sub-populations.

7th) The most frequent respiratory multimorbidities of NP patients (acute rhinosinusitis, asthma, and allergic rhinitis) as well as aspirin/NSAID intolerance were higher in severe than in non-severe patients.

Our study is based in medical records from the Catalan health care system at primary, hospital, or emergency care level which allowed the identification of a cohort of 30,189 adults with nasal polyps (CRSwNP), a 0.49% of the studied population in Catalonia. In addition, the prevalence by disease severity provides new original data not previously reported in epidemiological studies. This NP prevalence was lower than prevalence results reported in previous population-based studies (between 0.5% and 4.5%). There is limited evidence however on the prevalence of CRSwNP in general population-based studies, and results reported by the existing literature have to be taken carefully as they rely on random samples which are usually small and might not be representative of the whole general population. In addition, the diagnosis method used to identify individuals with CRSwNP seems to play an important role as prevalence results widely vary accordingly, being 1.3 - 4.3% when diagnosis was made using self-reported questionnaires [17,19], and 0.5 -2.7% when made using nasal endoscopy [18,20], which are more reliable. Yet, the prevalence results found in our study are more in line with studies using nasal endoscopy, although those studies rely on smaller samples such as 1,387 patients in Sweden [18], or 9,096 patients in South Korea [20].

In line with previous European studies from Sweden [18] and France [17], the prevalence of CRSwNP in Catalonia increased with age and for both males and females. Our study found a higher prevalence in males compared to females (1.45:1), slightly lower when compared to the findings (2.2:1) in the Swedish population [18].

This is the first epidemiological study attempting to define the severity of NP based on guideline recommended medical (OCS intake) and surgical (ESS), instead of reported sino-nasal symptoms by patients [17]. In addition, in severe NP the proportion of males is higher than females (1.6:1), the gender-gap increasing with age. Severe NP patients also tend to have a lower yearly income (< € 18,000) and be covered by a low co-payment rate (10%). Moreover, a higher prevalence of severe NP is found among male compared to female (0.15 vs. 0.09). Severe NP individuals also present higher blood eosinophil counts and serum total IgE levels as well as increased multimorbidities compared to non-severe individuals.

Concerning the therapeutic approaches for the overall adult population, intranasal corticosteroids were prescribed in almost all patients (85%), this being in accordance with the recommendations by international guidelines [1,4]. This is in line with findings in France (76.9%) [17], but even in a higher proportion. Although there is limited information in the literature, the use of oral corticosteroids was slightly higher with respect to that reported by Klossek et al. [17] (53.3% vs 42.5%, respectively). Antihistamines were found to be over-prescribed (65.3%), since they are not recommended in CRSwNP patients by international guidelines except for patients with concomitant allergic rhinitis (only 32% of patients in our NP cohort had allergic rhinitis).

The frequency of surgery was 15% of NP patients, similar to the 13.4% in the French study [17] and the nationwide surgery rates (0.71 per 1,000 people) reported in Finland [29]. The decision to undergo surgery is often shared between the patient and the surgeon. This implies that other factors different from the severity or control of symptoms could influence that decision. For instance, a severe patient could also prefer to avoid surgery if possible. There is also a lot of debate in the existing literature on the appropriate timing for surgery. Since the above points are not captured in the dataset, it has been assumed that surgery is performed in all patients who have been appointed for ESS. This assumption is based on EPOS 2020, which recommends the surgical option only when appropriate medical treatment (AMT) has failed and only for patients with more severe and uncontrol-

led forms of the disease.

New evidence is reported on type 2 biomarkers. Among individuals with available information, 83.8% showed type 2 inflammation. Specifically, 68.8% had a blood absolute eosinophil count ≥250 cell/µL, 83.2% a blood relative eosinophil count ≥2.5%, and 55.4% a serum total IgE value ≥100 KU/L. These are considered the relevant cut-off points to identify evidence of type-2 inflammation in patients with CRSwNP [1,30,31]. Although nasal polyp eosinophilia was not available from our dataset and these cut point values would need to be validated in different populations and real-life studies, our results are in line with recent literature findings where the proportion of type 2 inflammation on CRSwNP patients was 87% [32], and 85% [8] for patients in Europe and other western countries (US and Australia). Moreover, and in accordance with the existing literature [8], our results show significant evidence of a positive association between type 2 biomarkers and disease severity in CRSwNP and multimorbidities. Yet, we found higher values on all biomarkers for severe with respect to non-severe individuals (absolute blood eosinophils: 400 vs 310 Eos/µl; relative blood eosinophils: 5.4% vs 4.7%; and serum total IgE: 140 vs 108 KU/L), or with multimorbidities such as asthma (400 Eos/µl, 6.8% Eos, 137 KU/L, respectively) and aspirin/NSAID-intolerance (465 Eos/µl, 6.1% Eos, 128 KU/L, respectively) than for those without multimorbidities (300 Eos/µl, 4.1% Eos, 88.4 KU/L, respectively).

Respiratory and allergy multimorbidities are widely studied in the existing literature on CRSwNP and high frequencies found for asthma, acute rhinosinusitis, allergic rhinitis, aspirin/NSAID intolerance, atopic dermatitis, bronchiectasis, and food allergy. Some differences were found however when compared to similar studies. For instance, a higher proportion of asthma (40.1%) was found compared to France (26.1%) [17] but quite similar to two small studies previously done in Spain (36.6% and 48.9%) [33]. New information is provided for acute rhinosinusitis which was found in 41.1% of our NP cohort. Allergic rhinitis was reported in 32.1% of patients from our NP cohort this being lower than in previous studies (47.9%) [33]. Only 4.3% of NP patients were reported to have aspirin/NSAID intolerance, a much lower proportion compared to 20-28% prevalence reported in previous studies [17,33-35]. On the other hand, prevalence of AD (16.8%) is in a similar range than in another study in Spain (13.1%) [33] but lower than the French study (30.4%) [17]. Bronchiectasis were found in of the NP patients in a much lower proportion (2.9% vs 45%) compared to a previous study [36]. Concerning to food allergy, only was reported in 1% in our cohort, much lower than in the French study (21.9%) [17]. All these differences between studies may be due to several issues such as size of the cohort, severity of patients, or the type of diagnosis (CRS vs NP) which are prone to sampling error and lack of external validity.

New data are also provided in this study for systemic-general and psychiatric-neurological NP related multimorbidities: hypertension (33%), overweight (20.5%) with a similar result than a previous study (19) using BMI (27.9%), dyslipidaemia (11.2%), diabetes (10.8), and anxiety (18%). These are also significantly higher in severe vs. non-severe patients.

The main strength of this study is the large number of NP patients included in the cohort being able to include information on most of patients diagnosed with NP from the general adult population of Catalonia (6,155,980 adults) in 2017. This is also the first epidemiological study on NP (CRSwNP) conducted in Spain. Likewise, the inclusion of variables not used in previous studies such as prevalence of severity groups and type 2 inflammation are to be considered as important strengths of the present epidemiological study.

This study also has important limitations. First, given the lack of data on CRS symptomatology, the inclusion criteria for the presence of nasal polyps is based on medically diagnostic codes and not based on direct symptoms' assessment nor on endoscopy and/or imaging in the case of CRSwNP, which is the correct way to diagnose the disease recommended by current clinical guidelines [1]. Although one would expect medically certified diagnostic codes to follow a clinical assessment of symptoms, not having actual data on NP symptomatology could underestimate the prevalence results found in this paper due to a possible mismatch between medical records and sinonasal symptoms. Second, current diagnostic codes are old and need adaptation to new scientific terminology, as they cannot fully identify patients with CRS with or without nasal polyps. The low report (11%) of patients with chronic rhinosinusitis, when by definition CRS is intrinsic of the disease (CRSwNP) and affects all patients, still indicates a poor understanding of the disease by physicians who do not identify the main disease (CRS) as associated to NP [1, 4]. Thus, up-to-date specific diagnostic codes should be developed and used by medical doctors and institutions to correctly identify individuals with chronic rhinosinusitis with (CRSwNP) or without (CRSsNP) nasal polyps. In addition, miscoding could occur as some specialists could be assigned a different ICD-9 coding for CRS and CRSwNP such as those referring to chronic sinusitis. This could imply a possible underestimation of the prevalence results reported in this study. Therefore, physicians should be encouraged to properly use medically certified diagnoses in general and those for CRS and CRSwNP, in particular. Third, the retrospective nature of the study based on clinical history and the fact that severity of treatment is retrieved from prescribed medication and ESS instead of medical diagnosis. Fourth, we cannot disentangle whether drugs were prescribed to treat CRSwNP or other concomitant diseases, such as asthma. Therefore, using OCS intake as severity criteria might overestimate prevalence results for severe CRSwNP, and asthma might be a major confounder in assessing disease severity. On the other hand, the prevalence for severe NP patients could also be underestimated by assuming patients with no drug information present a mild NP which might or

might not be always the case. Moreover, drug prescription does not imply use or drug compliance. And fifth, the lack of inclusion of individuals that are diagnosed and treated outside of the statutory NHS, in private hospitals, or medical centres which could underestimate the prevalence and disease severity results.

Conclusions

This is the first large-scale population-based epidemiological study to study the prevalence of nasal polyps in Catalonia, Spain. Our findings show an overall prevalence of 0.49% for NP in the adult general population, these data being slightly lower than in previous studies. We acknowledge this result is based on information that is only derived from medical diagnoses that may underestimate or overestimate this prevalence. The disease is more prevalent in male than in female and increases over the life span. Moreover, new evidence is provided regarding biomarkers where higher values on blood eosinophils and total serum IgE were found in severe than non-severe individuals, as well as in patients with respiratory multi-morbidities, mainly asthma and aspirin/NSAID intolerance. Type 2 inflammation was found in 83.8% of the NP individuals with a higher frequency among severe (87.1%) than non-severe (82.7%) sub-populations. Finally, the most prevalent respiratory multi-morbidities were acute rhinosinusitis, asthma, and allergic rhinitis, all of them being more prevalent among severe than non-severe NP patients.

Authorship contribution

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

Conflict of interest

All the authors received specific funding for the development of 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. Authors on this manuscript have no relevant financial or other relationships to disclose.

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