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ORIGINAL ARTICLE

Rhinitis, Sinusitis, and Upper Airway Disease

Epidemiology and treatment of patients with Chronic rhinosinusitis with nasal polyps in Germany—A claims data study

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Abstract

Background: There are different levels of severity among patients who suffer from chronic rhinosinusitis with nasal polyps (CRSwNP). In this study, the epidemiology of CRSwNP and severe CRswNP was estimated.

Methods: A retrospective claim data analysis was conducted on adult CRSwNP patients (ICD-10: J33), and those classified as severe CRSwNP patients with inadequate disease control (based upon combinations of previous and current treatments) between 2015 and 2019. Prevalence and incidence figures were calculated and extrapolated to the German population. In addition, baseline characteristics and treatment outcomes were analysed.

Results: Overall, the 5-year prevalence of adult CRSwNP cases from 2015 to 2019 in Germany was 374,115 cases (about 5500 per million), with 12,989 (about 200 per million) patients being classified as severe CRSwNP with inadequate disease control, whereas 267,880 (about 3900 per million) patients were identified as having an incident CRSwNP diagnosis between 2016 and 2019. From the incident CRSwNP cohort, 80.55% had received at least one intranasal corticosteroid (INCS), 24.27% received at least 1 systemic corticosteroid (SCS), and 17.33% received at least one functional endoscopic sinus surgery (FESS) within 12 months after their incident diagnosis.

Conclusion: Severe CRSwNP with inadequate disease control affects about 200 per million people in Germany. INCS is the first-choice treatment for most CRSwNP patients; however, for patients with severe CRSwNP, SCS are prescribed more frequently and long-term effects of these should be further investigated, especially if despite treatment, adequate disease control cannot be achieved.

KEYWORDS
chronic rhinosinusitis with nasal polyps, claims data, epidemiology, Germany, nasal polyps

Abbreviations: ATC, anatomical therapeutic chemical classification system; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; ICD-10-GM, the international statistical classification of diseases and related health problems, 10th revision, German modification; INCS, intranasal corticosteroids; SCS, systemic corticosteroids.

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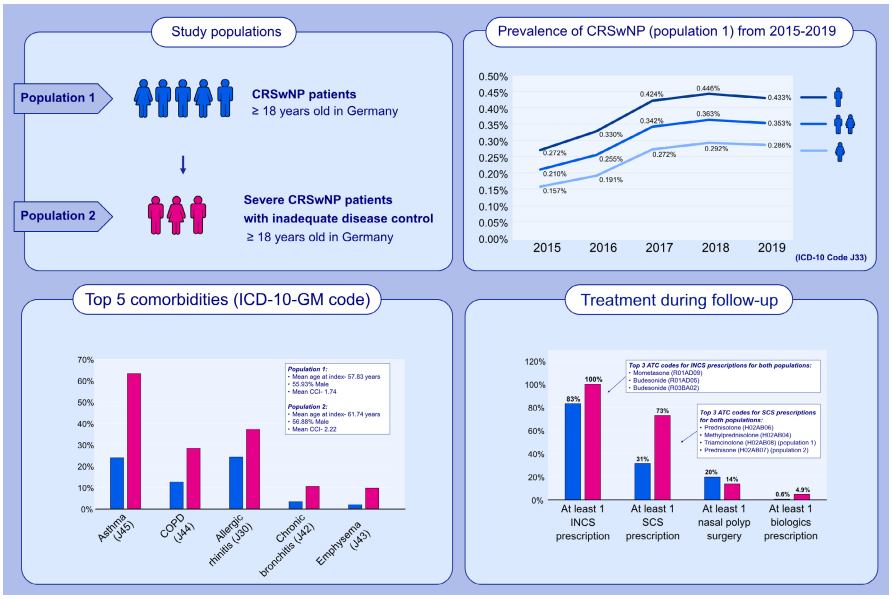

GRAPHICAL ABSTRACT

A German claims data analysis was conducted on adult CRSwNP patients and severe CRSwNP patients with inadequate disease control. The 5-year prevalence (2015–2019) of CRSwNP patients was about 5500 per million; 83.00% received INCS, 31.32% systemic corticosteroid SCS, and 19.73% surgery. Severe CRSwNP with inadequate disease control affects about 200 per million.

Abbreviations: ATC, anatomical therapeutic chemical classification system; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; ICD-10-GM, the international statistical classification of diseases and related health problems, 10th revision, German modification; INCS, intranasal corticosteroids; SCS, systemic corticosteroids

1 | BACKGROUND

Chronic rhinosinusitis (CRS) is a common disease, causing inflammation of the paranasal sinuses and nasal cavity associated with nasal obstruction/blockage accompanied by facial pain and sinus pressure.[1,2] The two main clinical phenotypes of CRS include CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Nasal polyps are defined as endoscopically visualized growths in the nasal cavity and paranasal sinuses, ultimately interfering with a patient's nasal passages and sinuses.[1,3] Nasal polyps are believed to affect up to 4% of the general adult population, and of those suffering from CRS, roughly 25–30% experience CRSwNP.[4-6]

There are various therapeutical options in place to treat CRSwNP with the goals of reducing inflammation of the paranasal sinuses, draining the nasal cavity and reducing the risk of sinus irritation.[7] These options include topical intranasal corticosteroids (INCS), systemic corticosteroids (SCS), aspirin desensitization and functional endoscopic sinus surgery (FESS) as standard therapy.[1,8] However, surgical procedures have shown a short-term efficacy of around 18 months to 4 years with a 10 – 60% risk for additional surgery due to nasal polyp regrowth and 79% over a 12-year period.[9-12]

However, there are different levels of severity among patients who suffer from CRSwNP and require adapted disease management. According to the European position paper on rhinosinusitis and nasal polyps (EPOS), SCS and FESS are primarily indicated for severe CRSwNP cases.[1,2,10] Moreover, patients who have a continued need for secondary therapy despite receiving INCS, SCS or FESS in the last year are considered as difficult to treat.[1,13] Patients with severe, uncontrolled forms of CRSwNP may be candidates for biological treatment.[2,7,9,14,15]

Principles for an optimal adapted disease management refer to broad data on severity grades and categories of disease control. Therefore, there is an important need for gaining population-based data on the prevalence, incidence, clinical characteristics and medical treatment of CRSwNP patients. This retrospective non-interventional claims data study aimed to estimate the prevalence and incidence of CRSwNP patients and severe CRSwNP cases with inadequate disease control in Germany and to describe these patients regarding baseline characteristics and treatments.

2 | METHODS

2.1 | Data Source and study population

This study is a retrospective non-interventional claims data study, which utilized an anonymized claims data set of approximately 3.4 million insured persons from two German regions, Saxony and Thuringia, provided by a German statutory health insurance fund (AOK PLUS). The database contained anonymized, patient-level data for the period 1 January 2015 to 31 December 2019 on drug prescriptions, procedures and surgical interventions, diagnoses and associated costs across outpatient and inpatient care facilities. The German statutory health insurance system covers all costs for physician visits, hospitalizations, medical interventions and prescription drugs. Only a minority of services (i.e. individual health services, over-the-counter medications) are

not covered and cannot therefore not be observed. Due to the anonymization of the data, approval by an ethics committee was not required. However, based on the analysis protocol, the permission of the data provider was obtained before data access was granted.

All patients with continuous enrolment to the sickness fund for the total study period (death as an exception) represented the basis for the analysis. Patients were defined based on diagnoses codes, documented according to the International Classification of Diseases and Related Health Problems, 10. Revision, German Modification ICD-10-GM; and based on outpatient medication prescriptions recorded, based upon the Pharmaceutical Central Number (PZN) and the Anatomical Therapeutic Chemical Classification system (ATC). Patients were selected for the base cohort of CRSwNP cases if they had either.

(i) At least two confirmed outpatient CRSwNP diagnoses (ICD-10 J33 'Nasal polyp') from an Ear–Nose–Throat (ENT) specialist in two different quarters within 12 months (M2Q criterion)
(ii) At least one inpatient primary CRSwNP diagnosis (ICD-10 J33)
(iii) At least one inpatient secondary CRSwNP diagnosis if CRS (ICD-10 J32 'Chronic sinusitis') was the primary diagnosis of the same hospital stay, or
(iv) At least two inpatient secondary CRSwNP diagnoses, between 1 January 2015 and 31 December 2019.

In addition, patients were required to be at least 18 years old at the time of the first observed diagnosis in above inclusion period.

Based upon the above-specified base cohort of CRSwNP patients, an additional *cohort of incident CRSwNP patients* was observed. To be included in this cohort, patients must have had a period of at least 12 months without prior CRSwNP diagnoses to the first observed (incident) CRSwNP diagnosis, which was defined as the index date (=wash-out period).

(i) Finally, a cohort of patients with severe CRSwNP and inadequate disease control was defined for 2019. For the purpose of this study, 'inadequately controlled' refers to patients with severe CRSwNP for whom previous therapy with SCS and/or FESS did not provide sufficient control. Accordingly, those patients have a continued need for secondary therapy. The definition is therefore not equivalent to the criteria of 'uncontrolled' therapy listed in EPOS 2020.[1] Therefore, as a proxy, a stepwise patient selection was implemented based on the assumption that a history of FESS or SCS in conjunction with current INCS consumption is associated with inadequately controlled severe CRSwNP if these patients are still in need for subsequent FESS or SCS. Step 1: Patients who fulfil the base cohort and were alive on 1 January 2019
(ii) Step 2: Patients received ≥3 INCS prescriptions in 2019 and visited an ENT specialist within the same quarter of prescriptions
(iii) Step 3: Patients had a prior treatment experience, defined as either (a) at least one SCS prescription in the same quarter of a CRSwNP diagnosis by an Ear–Nose–Throat (ENT) specialist within 24 months before the first INCS prescription in 2019; or (b) at least one FESS any time before the first INCS prescription in 2019
(iv) Step 4: Patients received ≥1 additional SCS prescription in the same quarter of a CRSwNP diagnosis by an Ear–Nose–Throat (ENT) specialist and/or FESS

If a patient fulfilled all four criteria, they were considered to have severe CRSwNP with inadequate disease control. The index date of these patients was defined as the first observed INCS prescription in 2019. To assess the impact of INCS prescriptions on the size of the selected patient population, a sensitivity analysis was conducted wherein *Step 2* required only 1 INCS prescription, instead of ≥3 INCS prescriptions. Moreover, three further subgroups according to the presence of specific comorbidities during the year 2019 (asthma, allergic rhinitis and COPD) were identified if the patient had at least 1 inpatient or 2 outpatient diagnosis.

2.2 | Outcomes and analyses

For the identified CRSwNP patients, the period prevalence was estimated once for each year of the study period (2015–2019) and once for the total 5-year period. Moreover, the cumulative incidence was analysed yearly (2016–2019; 2015 as wash-out period) for CRSwNP patients. For the cohort of severe CRSwNP patients with inadequate disease control, the prevalence was only estimated for the year 2019. All prevalence and incidence numbers were extrapolated to the German statutory health insurance (SHI) population (i.e. about 90% of entire population living in Germany; for example 73,009,237 people in 2019), using the KM6 statistic reported by the Federal Ministry of Health in Germany.[16] Moreover, results were also extrapolated to the entire population living in Germany utilizing data on the German population, as reported by the Federal Statistical Office of Germany based upon the census with 95% confidence intervals.[16,17] Age- and gender-specific prevalence and incidence figures from AOK PLUS were weighted using the respective age/gender distribution for the adult SHI and adult German population to account for differences between the dataset and the reference populations.

Baseline characteristics of patients, that is age, sex, Charlson comorbidity index (CCI) and additional comorbidities, were observed during a 12-month baseline period on or prior to the index date for the respective cohorts. In contrast, treatment (medication prescriptions and surgeries) was measured during the patient individual follow-up period for newly diagnosed CRSwNP patients and the cohort of severe CRSwNP cases with inadequate disease control. However, to observe the treatments of the latter patient cohort within a period of at least 12 months, the stepwise approach outlined above (step 1 – step 4) was modified by pushing each timeframe back one year respectively. Therefore, in Step 1, patients needed to be alive on 1 January 2018 (instead of 2019), and all INCS prescriptions in Step 2 were observed in 2018 (instead of 2019).

All outcomes were reported descriptively, based on the number and proportion of affected patients. Relevant codes can be found in

TABLE 1 Prevalence and Incidence of CRSwNP

	Prevalence of CRSwNP			Incidence of CRSwNP		
	Number of identified CRSwNP patients; and percentage from all adults in the database, who were alive at the beginning of the respective year					
Year	AOK PLUS *N* (%)	SHI *N* (%)	Germany *N* (%)	AOK PLUS *N* (%)	SHI *N* (%)	Germany *N* (%)
2015	4409 (0.21%)	113,817 (0.20%)	131,423 (0.20%)	-	-	-
2016	5260 (0.26%)	139,421 (0.24%)	160,348 (0.24%)	1726 (0.08%)	48,589 (0.08%)	60,457 (0.09%)
2017	6944 (0.34%)	190,183 (0.32%)	217,591 (0.32%)	2751 (0.14%)	79,419 (0.13%)	98,658 (0.15%)
2018	7245 (0.36%)	203,128 (0.34%)	231,346 (0.34%)	1769 (0.09%)	53,069 (0.09%)	65,960 (0.10%)
2019	6939 (0.35%)	195,157 (0.32%)	222,192 (0.33%)	1138 (0.06%)	34,283 (0.06%)	42,805 (0.06%)
5-year period (2015–2019)	11,479 (0.58%)	328,743 (0.55%)	374,115 (0.55%)	7384 (0.38%)	215,360 (0.36%)	267,880 (0.40%)

Note: Please note that due to a lack of disaggregated data for the age group 15–20 for the reference populations (SHI and German population), only those over the age of 20 were considered in this analysis.

TABLE 2 Stepwise patient selection for the cohort of severe CRSwNP with inadequate disease control

Step	Description	Main Analysis *N* (% of AOK PLUS)	Sensitivity Analysis *N* (% of AOK PLUS)
1	Patients with CRSwNP between 2015–2019, who are at least 18 years old at the time of their first observed diagnosis and alive on 1/1/2019	11,495 (0.58%)	11,495 (0.58%)
2	CRSwNP patients with ≥3 INCS prescriptions in 2019 (sensitivity: ≥1 one INCS prescription)	1859 (0.09%)	4647 (0.23%)
3	Patients who had a SCS prescription[a] and/ or FESS prior to the 1st INCS	630 (0.03%)	1381 (0.07%)
4	Patients who had a subsequent SCS[a]or FESS are described as those with inadequate disease control	395 (0.02%)	766 (0.04%)

[a]The SCS prescription was observed in the same quarter of a CRSwNP diagnosis by an Ear–Nose–Throat (ENT) specialist

Table A1. All analyses were carried out using Microsoft SQL Server 2019, Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA) and RStudio (R Studio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston).

3 | RESULTS

3.1 | Prevalence and Incidence of CRSwNP

In total, the 5-year prevalence of adult CRSwNP cases between 2015 and 2019 was 0.58% or about 5800 per million in the AOK PLUS database, that is 11,479 diagnosed cases. This resulted in 328,743 adult CRSwNP cases (95% confidence interval (CI): 327,624 – 329,865; about 5500 per million) in the SHI population and 374,115 cases (CI: 372,921– 375,312) in the German population after extrapolation. The prevalence increased during the observational period from about 2100 per million in 2015 to about 3500 per million in 2019, as seen in Table 1. Furthermore, the prevalence was higher among males (about 7200 per million) than females (about 4700 per million) throughout the 5-year prevalence. Among males, the age group-specific prevalence was highest between the ages 75 and 80 (about 11,500 per million), and among women, it was highest between the ages 60 and 65 (about 5900 per million) (Table A2).

For the cumulative incidence, 7384 patients who were newly diagnosed with CRSwNP were identified during 2016–2019. There was a noticeable increase in CRSwNP cases from 1726 (about 800 per million) in 2016 to 2751 (about 1400 per million) in 2017. It then decreased in 2018 to 1769 (about 900 per million) and further decreased in 2019 to 1138 (about 600 per million), as described in Table 1.

TABLE 3 Severe CRSwNP with inadequate disease control in 2019 extrapolated to SHI and German Population

	Main approach (≥3INCS prescriptions in step 2)			Sensitivity approach (≥1INCS prescription in step 2)		
Step	AOK PLUS *N* (%)	SHI *N* (%)	Germany *N* (%)	AOK PLUS *N* (%)	SHI *N* (%)	Germany *N* (%)
1	11,495 (0.58%)	329,461 (0.54%)	374,933 (0.54%)	11,495 (0.58%)	329,461 (0.54%)	374,933 (0.54%)
2	1859 (0.09%)	51,856 (0.08%)	59,302 (0.09%)	4647 (0.23%)	131,758 (0.21%)	150,148 (0.22%)
3	630 (0.03%)	18,085 (0.03%)	20,706 (0.03%)	1381 (0.07%)	40,118 (0.07%)	45,735 (0.07%)
4	395 (0.02%)	11,329 (0.02%)	12,989 (0.02%)	766 (0.04%)	22,030 (0.04%)	25,096 (0.04%)

TABLE 4 Baseline characteristics of observed cohorts

		Incident CRSwNP *N* = 7436 (AOK PLUS)	Severe CRSwNP with inadequate disease control in 2018 *N* = 269 (AOK PLUS)
Index Date		Incident CRSwNP diagnosis	First INCS prescription in 2018
Age at Index Date	Mean (SD)	57.83 (16.63)	61.74 (14.09)
Sex	Female (%) / Male (%)	44.07% / 55.93%	43.12% / 56.88%
CCI	Mean (SD)	1.74 (2.19)	2.22 (2.08)
Top Comorbidities (ICD-10-GM code)			
Asthma (J45)	*N* (%)	1773 (23.84%)	170 (63.20%)
COPD (J44)	*N* (%)	933 (12.55%)	76 (28.25%)
Allergic Rhinitis (J30)	*N* (%)	1796 (24.15%)	100 (37.17%)
Chronic Bronchitis (J42)	*N* (%)	242 (3.25%)	28 (10.41%)
Emphysema (J43)	*N* (%)	143 (1.92%)	26 (9.67%)

Note: Observed either on the patient specific index date or within 12 months prior.

3.2 | Prevalence of severe CRSwNP with inadequate disease control

From all CRSwNP patients who were alive on 1 January 2019, a total of 1859 patients were identified within the AOK PLUS database to have received at least three INCS prescriptions in 2019 (*Step 2*). Of these, 630 patients had records of a previous SCS prescription and/or FESS (*Step 3*). Ultimately, 395 patients had at least one follow-up SCS prescription in the same quarter of a CRSwNP diagnosis by an Ear–Nose–Throat (ENT) specialist or FESS and were classified as having severe CRSwNP with inadequate disease control in 2019 (*Step 4*). Compared with this figure, the sensitivity analysis considered patients with at least one INCS prescription instead of at least three prescriptions revealed a number of 766 severe CRSwNP patients with inadequate disease control. Table 2 outlines how many patients were included for each step.

After extrapolation of the numbers of severe CRSwNP patients with inadequate disease control, 11,329 patients (CI: 11,122 – 11,539; about 200 per million) in the SHI population and 12,989 patients (CI: 12,768 – 13,215) in the German population can be expected. In contrast, the sensitivity analysis requiring only one INCS prescription led to extrapolated figures of 22,030 (CI: 21,741 – 22,322; about 400 per million) in the SHI population and 25,096 (CI: 24,788 – 25,408) in the German population as seen in Table 3.

3.3 | Patient characteristics

Approximately 55.93% of incident CRSwNP patients were male, and the average age of this population at the time of the incident diagnosis was 57.80 years. As for the patients with severe CRSwNP with inadequate disease control, 56.88% were male, and the average age was 61.74 years. The second cohort had a higher disease severity as described in Table 4.

3.4 | Treatment of incident CRSwNP patients

Out of 7436 incident CRSwNP patients[1], 83.00% (*N* = 6172) received at least one INCS prescription over an average period of 803 days of follow-up after their incident diagnosis; 45.86% (*N* = 3410) received their first INCS prescription on the day of their initial diagnosis. For the entire follow-up period, patients received on average 1.86 INCS prescriptions per patient-year (ppy) and thus medication for an average of 90.47 days (ppy).

[1]The patient count within this cohort (*N* = 7436) is different to the count presented in Table 1 (*N* = 7384), because the cohort with 7384 patients represents those over the age of 20 (instead of 18) due to the lack of disaggregated data for the age group 15–20 years in the reference populations. However, the cohort with 7436 patients includes patients from the age of 18 years or older.

TABLE 5 Top agents prescribed from the index date until 31/12/2019 for incident CRSwNP cohort

Prescription	Top 3 ATC Codes	Number of patients (*N* = 7436)	Proportion
INCS	Mometasone (R01AD09)	4173	56.12%
	Budesonide (R01AD05)	1944	26.14%
	Budesonide (R03BA02)	558	7.50%
SCS	Prednisolone (H02AB06)	1649	22.18%
	Methylprednisolone (H02AB04)	470	6.32%
	Triamcinolone (H02AB08)	216	2.90%
Targeted Asthma and COPD Therapies	Salbutamol (R03AC02)	1311	17.63%
	Formoterol and Budesonide (R03AK07)	493	6.63%
	Formoterol and Beclometasone (R03AK08)	469	6.31%
Biological therapies	Mepolizumab (R03DX09)	22	0.30%
	Benralizumab (R03DX10)	12	0.16%
	Omalizumab (R03DX05)	9	0.12%
Other non-respiratory therapies	Cefuroxime (J01DC02)	1554	20.90%
	Doxycycline (J01AA02)	816	10.97%
	Clindamycin (J01FF01)	710	9.55%
FESS	Endonasal Pansinus Operation	1081	14.54%
	Nasal Polyps Removal	176	2.37%
	Ethmoidectomy: Polyp removal	156	2.10%

Note: Please note that the dataset does not contain information on the underlying cause or condition for the respective prescription, only the date the prescription was filled. Therefore, the treatments outlined above might not be direct treatments of CRSwNP, but with an additional comorbidity.

TABLE 6 Top agents prescribed from the index date until 31/12/2019 for severe CRSwNP with inadequate disease control cohort

Prescription	Top 3 ATC Codes	Number of patients (*N* = 269)	Proportion
INCS	Mometasone (R01AD09)	197	73.23%
	Budesonide (R01AD05)	64	23.79%
	Budesonide (R03BA02)	46	17.10%
SCS	Prednisolone (H02AB06)	158	58.74%
	Methylprednisolone (H02AB04)	39	14.50%
	Prednisone (H02AB07)	25	9.29%
Targeted Asthma and COPD Therapies	Salbutamol (R03AC02)	115	42.75%
	Formoterol and Budesonide (R03AK07)	53	19.70%
	Salmeterol and Fluticasone (R03AK06)	49	18.22%
Biological therapies	Mepolizumab (R03DX09)	6	2.23%
	Omalizumab (R03DX05)	3	1.12%
	Benralizumab (R03DX10)	3	1.12%
Other non-respiratory therapies	Cefuroxime (J01DC02)	58	21.56%
	Amoxicillin and beta-lactamase inhibitor (J01CR02)	33	12.27%
	Clindamycin (J01FF01)	30	11.15%
FESS	Multiple paranasal sinuses operation	32	11.90%
	Ethmoidectomy: Polyp Removal	3	1.12%
	Polyp removal	2	0.74%

Note: Table A3 provides information on the medication of patients, stratified by the top 3 comorbidities.

Please note that the dataset does not contain information on the underlying cause or condition for the respective prescription, only the date the prescription was filled. Therefore, the treatments outlined above might not be direct treatments of CRSwNP, but with an additional comorbidity.

Additionally, 31.32% (*N* = 2329) of patients received a SCS prescription within the follow-up period, with an average of 0.35 prescriptions ppy, accounting for 16.14 days of coverage, whereas only 0.58% (*N* = 43) were prescribed biologics, with an average of 0.02 ppy, accounting for 1.12 days of coverage. As the first biologic for the treatment of severe CRSwNP and inadequate disease control was only approved in October 2019, the prescription of biologics in this context is likely due to comorbidities, such as asthma (see Table 4). Furthermore, 19.73% (*N* = 1467) of patients received at least one FESS in the follow-up period. Overall, 48.09% received their first INCS or SCS prescription on their original diagnosis date; within the first 12 months, 87.05% have received treatment with either INCS, SCS or FESS. Table 5 outlines the agents most often prescribed to patients.

3.5 | Treatment of patients with severe CRSwNP and inadequate disease control

On average, patients with severe CRSwNP and inadequate disease control in 2018 (*N* = 269) received 5.33 INCS prescriptions ppy, accounting for 267.74 days of coverage during the follow-up period until 31 December 2019. Moreover, 72.86% (*N* = 196) of these patients received SCS prescriptions within the follow-up period (667 days). On average, 1.47 SCS prescriptions ppy with 67.96 days of coverage were identified, whereas only 4.83% (*N* = 13) patients received biologics, with an average of 0.19 prescriptions ppy and 10.50 days of coverage. In addition, 13.75% (*N* = 37) of patients underwent surgical intervention. Table 6 outlines the most common agents received by patients during the follow-up period. Additionally, since it is not possible to identify the disease or indication associated with a medication prescribed to a patient, treatment was also observed for patient subgroups with selected respiratory comorbidities (asthma, allergic rhinitis and COPD) outlined in Table A3.

4 | DISCUSSION

To the best of our knowledge, there are only a few studies that have described the epidemiology of CRSwNP patients and this is the first study to describe treatment of CRSwNP patients with a subset of patients with severe CRSwNP and inadequate disease control in Germany, utilizing a large real-world dataset, which represents about 4.4% of the statutory insured population.[18-20]

The five-year prevalence of diagnosed CRSwNP in adults was found to be 5800 per million in the dataset used, corresponding to a proportion of 5500 per million in the total population of adults in Germany. Therefore, the estimation of this study is at the lower limit of prevalence figures reported in other studies, which estimated CRSwNP affects up to 4% or 40,000 per million of the general adult population.[4-6,21-23] This result can be explained, among other things, by the fact that the study is based on the accepted approach of counting patients in the outpatient setting only after at least two confirmed diagnoses within 365 days. Furthermore, only diagnoses of ENT specialists were considered in this study. Consequently, the chosen approach could result in a lower estimate than compared with a different methodology or data source. However, to date, there is a noticeable lack of solid and representative data on the prevalence of CRSwNP for Europe but especially for Germany, making it difficult to draw conclusions from the epidemiological figures presented, due to a lack of comparability.[2,24] In line with other studies, it was discovered that CRSwNP is more common in males (6500 per million) than in females (4700 per million) and that the highest prevalence was observed within the 65 to 80 age range.[21,22] Furthermore, it was found that asthma (23.84%) and allergic rhinitis (24.15%) were the most commonly reported comorbidities, which is consistent with previous studies reporting a proportion of 23–50% of CRSwNP patients to be affected by asthma.[11,25,26]

Importantly, it was found that 0.02% of patients from the database had severe CRSwNP with inadequate disease control, resulting in an extrapolated number of 11,329 total cases (200 per million) in the SHI population and 12,989 total cases in the population living in Germany. However, since the estimation relies on assumptions and proxies applied during the stepwise patient selection, prevalence figures are sensitive to these assumptions. Consequently, within the conducted sensitivity analysis, the estimated numbers increased to 22,030 (400 per million) and 25,096 for SHI and Germany, respectively, if only at least one INCS prescription (rather than at least three) was required for selection. Nevertheless, the estimates are comparable with figures reported in another study conducted in 2017, that used a similar definition for severe CRSwNP patients with inadequate disease control,[19] and concluded that a total of 11,492 patients in the SHI population and 13,393 in the population in Germany are affected. However, there are differences between both studies such as methodology, study period and data source that need to be accounted for when making comparisons.

For the treatment of newly diagnosed CRSwNP patients, it was observed that 83.00% received a prescription of an INCS within the follow-up period of approximately two years. However, 45.86% received their first prescription already at the time of their first diagnosis. Thus, INCS is often used as a first-choice treatment in CRSwNP patients, that aligns with national guidelines in Germany.[2] In contrast, the proportion of patients prescribed SCS (31.32%) was lower. Conversely, out of the patients identified to have severe CRSwNP and inadequate disease control, a higher share of patients (72.86%) received SCS treatment, which in turn is also consistent with the European position paper that SCS should be considered as an intermittent treatment option in more severe CRSwNP cases.[1,10] Moreover, according to the guideline, FESS can be considered as a treatment option for patients with CRSwNP if conservative pharmacological interventions fail.[2] Within this study, it was observed that 19.73% of the CRSwNP patients received FESS within approximately two years after their first CRSwNP diagnosis. Studies from other European countries reported a higher percentage of patients who had undergone surgery (46–85%).[27-29] However, figures varied across countries, and a comparison of findings seems limited due to the differences in healthcare systems and clinical practices.

4.1 | Limitations

The utilized dataset contains data from routine practice, that is primarily collected for billing and reimbursement purposes. Claims datasets are considered a powerful source for pharmacoepidemiology and health services research, as they include complete information on patients' diagnostics and prescribed treatments across different care settings, both in the inpatient and outpatient care. The use of an extensive real-world database provided this study with reliable data. However, there are some limitations associated with this study that we acknowledge.

First, the reported epidemiological figures considered only documented diagnosis. Therefore, data could be missing or subject to coding errors. Nonetheless, the coding in the database is considered to be of high quality,[30,31] as is the external validity, given the importance of adequate documentation for reimbursement of services. However, since there is no exact ICD-10-GM code for CRSwNP, the study relied on the assumption that the ICD-10 GM code J33 for nasal polyps accurately identified respective patients and that it was correctly used by physicians, which is in line with other claims data studies.[18,20] For this reason, prior to the analysis, the number of patients diagnosed with J32 (chronic sinusitis) and/or J33 (nasal polyps) was compared and evaluated in discussion with an expert, with the conclusion to use J33, as J32 could have led to an overestimation. Additionally, the study only considered patients diagnosed with J33 from an ENT specialist, which was also implemented to ensure the diagnosis was correct and avoid overestimation.

Secondly, concerning the medications examined in this study, it should be stated that there may be a lack of reporting of pharmacological interventions applied within the inpatient setting and other interventions which do not qualify for medical claims (i.e. over-the-counter medication). Additionally, within the database, there is no direct association between a drug prescription and a diagnosis. Therefore, it is difficult to identify whether medication prescriptions are associated with CRSwNP or other comorbidities such as asthma or analgesic intolerance, which were common comorbidities. Even if diagnoses and prescriptions can be clearly allocated at the quarterly level, limited information is available regarding the exact diagnosis date per quarter (i.e. documented start date of the reimbursement of a physician's provided care per diagnosis). Thus, the reported number of CRSwNP patients with INCS prescription on the same day as their diagnosis may be biased.

Thirdly, another limitation regarding the definition of severe CRSwNP cases with inadequate disease control was that the patient selection relies on proxies to measure the severity of disease and inadequacy of disease control since relevant clinical information were missing in the dataset. Even though the methodology was quite similar to a comparable investigation[19] and definitions derived from literature, the stepwise approach might limit external validity, which was not tested in this study. Consequently, the patient selection might have been biased and may not fully represent the actual population of patients with severe CRSwNP with inadequate disease control. Additionally, the model assumed an SCS prescription that occurs in the same quarter as the CRSwNP diagnosis is attributed to the CRSwNP. This may lead to overestimation, as the SCS administration may also have been prescribed for some other indication. However, to mitigate this limitation, we have consulted with clinical experts, who validated the stepwise approach.

Finally, it must be noted that extrapolation from the AOK PLUS dataset to the SHI population and population in Germany could only be conducted for adults 20 years or older for the observational years due to the lack of detailed data for the age group 15–20 from the representative populations (SHI and German). Therefore, to ensure accurate estimations, 18- and 19-year-old patients were omitted. However, they only represented a small proportion of the affected patient cohort. In addition, more precise data on the age breakdown were available for the German population in 2019. Thus, the proportion of 18- to 19-year-olds from this cohort was transferred to the SHI population to enable the most accurate extrapolation possible for this age group for the year 2019.

5 | CONCLUSIONS

This analysis based on a large real-world representative dataset of the statutory insured population demonstrated that CRSwNP affects about 5500 per million of the total population of adults in Germany, with a higher prevalence among males. Severe CRSwNP with inadequate disease control affects about 200 per million within the population. Those patients often suffer from concomitant respiratory disease, that has an impact on the choice of the treatment strategy. In alignment with the current treatment recommendation, INCS is the first-choice treatment for most patients with CRSwNP, and SCS was only prescribed in the minority of patients. However, for patients with severe CRSwNP, in addition to INCS, SCS are prescribed more frequently, and the long-term effects of these should be considered, especially if adequate control cannot be achieved despite treatment with INCS and SCS.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

A.S., F.H, J.W., B.U., M.W. and M.R. designed the study design and protocol and T.W., U.W. and O.P. provided constructive feedback and comments from a technical perspective. A.S. and F.H. conducted the data analysis and all authors assisted in interpreted the findings. A.S. took lead in writing the manuscript with the guidance of F.H. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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REFERENCES

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Off J Eur Int Rhinol Soc Confed Eur ORL-HNS*. 2020;58:55.
2. Vogelmeier C, Buhl R, Burghuber O, et al. Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD). *Pneumologie*. 2018;72(04):253-308. doi:10.1055/s-0043-125031
3. Newton JR, Ah-See KW. A review of nasal polyposis. *Ther Clin Risk Manag*. 2008;4(2):507-512. doi:10.2147/tcrm.s2379
4. Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2016;4(4):565-572. doi:10.1016/j.jaip.2016.04.012
5. Rajguru R. Nasal polyposis: current trends. *Indian J Otolaryngol Head & Neck Surg*. 2014;66(S1):16-21.
6. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal AEH. Prevalence of nasal polyposis in France: a cross-sectional, case–control study. *Allergy*. 2005;60(2):233-237.
7. Howard B, Lal D. Oral steroid therapy in chronic rhinosinusitis with and without nasal polyposis. *Curr Allergy Asthma Rep*. 2013;13(2):236-243.
8. Pfaar O, Klimek L. Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements. *Allergy Clin Immunol*. 2006;6(3):161-166.
9. Bachert C, Sousa AR, Lund VJ, et al. Rhinitis, sinusitis, and ocular allergy Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. *J Allergy Clin Immunol*. 2017;140(4):1024-1031.
10. Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of disease in chronic rhinosinusitis with nasal polyps. *J Asthma Allergy*. 2021;14:127-134. doi:10.2147/JAA.S290424
11. Calus L, Van Bruaene N, Bosteels C, et al. Twelve-year follow-up study after endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyposis. *Clin Transl Allergy*. 2019;9(1):1-11. doi:10.1186/s13601-019-0269-4
12. Catherine A, Loftus MS, Soler ZM, et al. Revision surgery rates in chronic rhinosinusitis with nasal polyps: meta-analysis of risk factors. *Allergy Rhinol*. 2019;10(2):199-207.
13. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;59:1-12.
14. Bachert C, Gevaert P, Hellings P. Biotherapeutics in Chronic Rhinosinusitis with and without Nasal Polyps. *J Allergy Clin Immunol Pract*. 2017;5(6):1512-1516. doi:10.1016/j.jaip.2017.04.024
15. Ren L, Zhang N, Zhang L, Bachert C. Biologics for the treatment of chronic rhinosinusitis with nasal polyps - state of the art. *World Allergy Organ J*. 2019;12(8):100050.
16. Federal Ministry of Health: Report on the development of personnel and administrative costs in the SHI system 2019. Results of the SHI statistics KG1/ 2019 and CY1/ 2019.
17. OV Daten des Gesundheitswesens 2010. Published online 2020:1-161. https://www.bundesgesundheitsministerium.de/service/publikationen/einzelansicht.html?tx_rsmpublications_pi1%5Bpublication%5D=48&tx_rsmpublications_pi1%5Baction%5D=show&tx_rsmpublications_pi1%5Bcontroller%5D=Publication&cHash=9de8089e874b06db2fd899fb2d5720
18. Park J-H, Seidel J, Bachert DU, Claus Dazert S, Kostev K. Medication use in patients with chronic rhinosinusitis in Germany - a large retrospective patient-based study. *Rhinology J*. 2018;18:55.
19. Gmbh SD. Dossier zur Nutzenbewertung gemäß § 35a SGB V Modul 3 D Patienten mit schwerer chronischer Rhinosinusitis mit Inhaltsverzeichnis. Published online. 2019.
20. Ference EH, Reddy SR, Tieu R, Gokhale S, Park S, LeCocq J. Burden of Nasal Polyps in the United States. *OTO Open*. 2020;4(3):2473974X2095072.
21. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and risk factors of chronic rhinosinusitus, allergic rhinitis, and nasal septal deviation results of the Korean national health and nutrition survey 2008–2012. *JAMA Otolaryngol - Head Neck Surg*. 2016;142(2):162-167. doi:10.1001/jamaoto.2015.3142
22. Kim DH, Han K, Kim SW. Effect of chronic rhinosinusitis with or without nasal polyp on quality of life in South Korea: 5th Korea national health and nutrition examination survey Korean. *Clin Exp Otorhinolaryngol*. 2016;9(2):150-156. doi:10.21053/ceo.2015.01053
23. WRAY. Chronic rhinosinusitis with nasal polyps. *Physiol Behav*. 2017;176(5):139-148. doi:10.1016/j.physbeh.2017.03.040
24. Chen S, Zhou A, Emmanuel B, Thomas K, Guiang H. Systematic literature review of the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyposis. *Curr Med Res Opin*. 2020;36(11):1897-1911. doi:10.1080/03007995.2020.1815682
25. Hunter T, DeConde A, Manes R. Disease-related cost burden in patients undergoing sinus surgery for chronic rhinosinusitis: a claims-based analysis. *Value Heal*. 2017;20(9):A644. doi:10.1016/j.jval.2017.08.1485
26. Shamji MH, Thomsen I, Layhadi JA, et al. Broad IgG repertoire in patients with chronic rhinosinusitis with nasal polyps regulates proinflammatory IgE responses. *J Allergy Clin Immunol*. 2019;143(6):2086-2094.e2. doi:10.1016/j.jaci.2019.02.001
27. Kwon Y, Bell TJ, Solem C, et al. Quality-Adjusted Survival for Low-Dose Cytarabine (LDAC) Versus Glasdegib+LDAC among newly diagnosed acute myeloid leukemia patients who are not

candidates for intensive chemotherapy: A Q-TWiST analysis. *Blood*. 2019;134(Supplement_1):2610.
28. Khan A, Vandeplas G, Huynh TMT, et al. The Global Allergy and Asthma European Network (GALEN) rhinosinusitis cohort: A large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. *Rhinology*. 2019;57(1):32-42. doi:10.4193/Rhin17.255
29. Philpott C, Hopkins C, Erskine S, et al. The burden of revision sinonasal surgery in the UK-data from the Chronic Rhinosinusitis Epidemiology Study (CRES): a cross-sectional study. *BMJ Open*. 2015;5(4):e006680. doi:10.1136/bmjopen-2014-006680
30. Langner I, Ohlmeier C, Zeeb H, Haug U, Riedel O. Individual mortality information in the German Pharmacoepidemiological Research Database (GePaRD): A validation study using a record linkage with a large cancer registry. *BMJ Open*. 2019;9(7):1-7. doi:10.1136/bmjopen-2018-028223
31. Hartmann J, Weidmann C, Biehle R. Validierung von GKV-Routinedaten am Beispiel von geschlechtsspezifischen Diagnosen. *Das Gesundheitswesen*. 2016;78(10):e53-e58.

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APPENDIX A

TABLE A1 List of ATC and OPS codes

Type	Treatment	ATC Code (outpatient)	OPS Codes (inpatient)
Intranasal Corticosteroids	Beclometasone	R01AD01; R03BA01	-
	Flunisolide	R01AD04	-
	Budesonide	R01AD05; R03BA02	-
	Betamethasone	R01AD06	-
	Fluticasone	R01AD08; R03BA05	-
	Mometasone	R01AD09	-
	Triamcinolone	R01AD11	-
	Fluticasonfuroat	R01AD12	-
	Fluocortin	R01AD21	-
	Dexamethasone (Combination)	R01AD53	-
	Fluticasone (Combination)	R01AD58	-
	Ciclesonide	R01AD13	-
Systemic Corticosteroids	Methylprednisolone	H02AB04	-
	Paramethasone	H02AB05	-
	Prednisolone	H02AB06	-
	Prednisone	H02AB07	-
	Triamcinolone	H02AB08	-
	Hydrocortisone	H02AB09	-
	Cortisone	H02AB10	-
	Betamethasone-Depot	H02AB51	-
	Methylprednisolone-Depot	H02AB54	-
	Prednisolone-Depot	H02AB56	-
	Triamcinolone-Depot	H02AB58	-
FESS	Ethmoidectomy: Polyp removal, sphenoid sinus	-	5–222.20
	Nasal Polypectomy	-	5–212.2
	Ethmoidectomy, endonasal (With representation of the skull base)	-	5–222.21
	Multiple paranasal sinuses, endonasal [With representation of the skull base (endonasal pansinus operation)]	-	5–224.63
	Multiple paranasal sinuses, endonasal [With supply to the skull base]	-	5–224.64
	Combination of at least two of the following surgeries	-	5–221.6, 5–222.2, 5–222.4, 5–223.5

TABLE A1 (Continued)

Type	Treatment	ATC Code (outpatient)	OPS Codes (inpatient)
Additional targeted asthma and COPD therapy	Leukotriene receptor antagonists	R03DC-	-
	Tiotropium bromide (LAMA)	R03BB04	
	Selective beta−2-adrenoreceptor agonists (LABA)	R03AC-	-
	Adrenergics in combination with corticosteroids or other drugs (LABA+INCS)	R03AK-	-
	Theophylline	R03DA04	-
	Ipratropium Bromide	R03BB01	-
	Vilanterol and umeclidinium bromide (LABA+LAMA)	R03AL03	-
	Indacaterol and glycopyrronium bromide (LABA+LAMA)	R03AL04	-
	Formoterol and aclidinium bromide (LABA+LAMA)	R03AL05	-
	Olodaterol and tiotropium bromide (LABA+LAMA)	R03AL06	-
Biologics	Dupilumab	D11AH05	-
	Mepolizumab	R03DX09	-
	Reslizumab	R03DX08	-
	Benralizumab	R03DX10	-
	Omalizumab	R03DX05	-
Other non-respiratory therapies	Antihistamines for systemic use	R06A-	-
	Decongestants and antiallergics	S01G-	-
	Antibacterial for systemic use	J01-	-

TABLE A2 5-year Prevalence of CRSwNP from 1/1/2015-31/12/2019 in the German Population by Gender (*N*, %)

	2019		
Age Groups	Male (*N* = 33,147,064)	Female (*N* = 34,689,145)	Total (*N* = 67,836,209)
20 until 25 years	3870 (0.16%)	3653 (0.17%)	7523 (0.16%)
25 until 30 years	6475 (0.25%)	6962 (0.29%)	13,437 (0.26%)
30 until 35 years	11,080 (0.39%)	9668 (0.36%)	20,748 (0.38%)
35 until 40 years	10,471 (0.39%)	9794 (0.38%)	20,265 (0.38%)
40 until 45 years	13,766 (0.56%)	12,289 (0.50%)	26,055 (0.53%)
45 until 50 years	14,944 (0.56%)	13,511 (0.51%)	28,455 (0.54%)
50 until 55 years	22,886 (0.68%)	18,091 (0.54%)	40,978 (0.61%)
55 until 60 years	25,278 (0.75%)	18,573 (0.55%)	43,851 (0.65%)
60 until 65 years	23,708 (0.85%)	16,948 (0.59%)	40,657 (0.72%)
65 until 70 years	21,563 (0.93%)	14,365 (0.56%)	35,927 (0.74%)
70 until 75 years	17,863 (1.04%)	11,149 (0.57%)	29,012 (0.79%)
75 until 80 years	19,873 (1.15%)	12,423 (0.58%)	32,296 (0.83%)
80 and older	22,411 (1.04%)	12,499 (0.36%)	34,911 (0.61%)
All age groups	214,190 (0.65%)	159,925 (0.46%)	374,115 (0.55%)

TABLE A3 Subgroups of Severe CRSwNP patients with inadequate disease control based on specific comorbidities during the baseline period

	Asthma (J45) *N* = 170	Allergic Rhinitis (J30) *N* = 100	COPD (J44) *N* = 76
INCS			
Number of patients (%)	170 (100%)	100 (100%)	76 (100%)
Number of prescriptions ppy	5.43	5.41	5.29
Mean (SD) of prescriptions	10.02 (4.64)	9.97 (4.07)	9.79 (4.44)
DDD of prescriptions ppy	276.93	269.25	274.21
SCS			
Number of patients (%)	136 (80.0%)	77 (77.0%)	65 (85.53%)
Number of prescriptions ppy	1.71	1.54	2.09
Mean (SD) of prescriptions	3.14 (3.21)	2.82 (3.04)	3.87 (3.58)
DDD of prescriptions ppy	81.88	69.86	106.02
FESS			
Number of patients (%)	17 (10.0%)	12 (12.0%)	12 (15.79%)
Number of surgeries ppy	0.07	0.09	0.12
Mean (SD) of surgeries	0.13 (0.46)	0.16 (0.49)	0.22 (0.61)
Biologics			
Number of patients (%)	13 (7.65%)	7 (7%)	4 (5.26%)
Number of prescriptions ppy	0.3	0.18	51
Mean (SD) of prescriptions	0.54 (2.61)	0.34 (1.35)	0.68 (3.55)
DDD of prescriptions ppy	16.74	14.46	14.06
Targeted Asthma and COPD Therapy			
Number of patients (%)	165 (97.06%)	85 (85%)	76 (100%)
Number of prescriptions ppy	5.59	4.76	7.20
Mean (SD) of prescriptions	10.34 (8.16)	8.84 (8.26)	13.32 (8.34)
DDD of prescriptions ppy	379.74	323.33	491.61
Additional non-respiratory Therapy			
Number of patients (%)	131 (77.06%)	74 (74%)	49 (64.47%)
Number of prescriptions ppy	1.13	1.14	0.88
Mean (SD) of prescriptions	2.07 (2.34)	2.09 (2.10)	1.60 (2.25)
DDD of prescriptions ppy	18.27	22.35	11.60

Note: Average follow-up period for the Asthma cohort was 663 days, Allergic Rhinitis was 665 days and COPD was 664 days. Additionally, these subgroups are not mutually exclusive.