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GALEN Rhinosinusitis Cohort methodology

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Title

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

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SUMMARY (195 words; max 200 words)

Background: Chronic rhinosinusitis (CRS) is a common yet under-recognised chronic inflammatory disease of the nose and paranasal sinuses that is classified according to the presence (CRSwNP) or absence (CRSsNP) of nasal polyps.

Methodology/Principal: This paper reports the methodology and descriptive results of the Global Allergy and Asthma European Network (GALEN) rhinosinusitis cohort. We established a large CRS cohort within the GALEN consortium (European FP6 research initiative) to identify inflammatory endotypes, the natural disease course, and its impact on health-related quality of life (HRQoL). Detailed information on the impact of CRS on HRQoL, comorbidity incidence, objective disease measures, and medical and surgical

treatments were collected.

Results: This multicentre cross-sectional case-control study recruited 935 adults (869 eligible for analysis: 237 CRSsNP; 445 CRSwNP; 187 controls [reference group]). Comorbidities such as asthma, allergy, eczema, food allergy, urticaria, and chronic obstructive pulmonary disease were significantly more frequent in CRS patients. Nasal corticosteroids, antibiotics, and oral corticosteroids were the most common treatments. Significantly more CRSwNP patients reported previous sinonasal surgery.

Conclusions: This study provides detailed information that facilitates studying CRS and its main phenotypes. However, patient distribution of this study does not necessarily reflect disease distribution in the general population.

Key words: rhinitis, sinusitis, nasal polyps, cross-sectional studies, cohort studies

Introduction

Chronic rhinosinusitis (CRS) is a common yet under-recognised chronic inflammatory disease. The prevalence of CRS in various European countries ranges from 7 to 27%, with an average of 10.9% [1]. A recent study in the United States estimated that prevalence of CRS in the source population was 11.9%; while another 17.0% met criteria for past CRS [2].

CRS is pragmatically classified according to the presence (CRSwNP) or absence (CRSsNP) of nasal polyps (NP). Using patient questionnaires to measure the prevalence of NP yielded estimates of 2.1% (France) [3] to 4.3% (Finland) [4] in Europe and 1.1% in China [5].

Although the aetiology of CRSwNP is largely unknown, CRSsNP and CRSwNP are associated with T-cell-mediated immune responses. CRSsNP is mostly characterised by fibrosis and mild inflammation, and is often associated with Th1 or Th17 inflammation. CRSwNP appears to be associated with moderate or severe Th2 eosinophilic inflammation [6–8]. However, recent studies suggest that the molecular diversity of patients with CRS is not reflected by simple differentiation into Th1 and Th2 disease categories [6].

According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines [9], patients diagnosed with CRS must have $\geq$ 2 of the following symptoms: mucopurulent drainage, nasal obstruction, facial pain or pressure, and partial (hyposmia) or total (anosmia) loss of smell; and at least one of the following objective measures: documentation of inflammation by mucopurulent drainage, presence of NP and/or radiographic imaging showing occupation of paranasal sinuses. Considerable overlap exists between the symptoms associated with CRSwNP and CRSsNP [10]. Similar symptomatology has been observed between the two groups. However, patients with CRSwNP score more frequently and significantly higher on nasal symptoms such as rhinorrhoea, nasal congestion

94 or obstruction, and olfactory deficits (the most discriminant symptom is loss of smell)
95 compared with those with CRSsNP [8, 10], who more frequently report facial pain [11].

96 There are reported associations between CRSwNP and other comorbidities, with asthma being
97 the most common comorbid disease in this population. Up to 66.7% (range 34.0–66.7%) of
98 patients with CRSwNP also suffer from asthma [10, 12–15]. It has also been suggested that up to
99 25% of CRSwNP patients may have undiagnosed asthma [16]. Studies have also demonstrated
100 an association between CRSwNP and non-steroidal anti-inflammatory drug (NSAID)
101 hypersensitivity [17–21]. About 15% of CRSwNP patients have NSAID hypersensitivity [17]. A
102 significant impact on health-related quality of life (HRQoL) has been demonstrated in several
103 studies in adults with CRSwNP compared with both the general population and patients with
104 CRSsNP [22–24].

105 There are multiple published international guidelines for the treatment of CRS, including a
106 European position paper [9] and an international consensus statement [25]. CRS treatment aims
107 to achieve and maintain disease control [26]. Disease control is reached when patients do not
108 have symptoms or have symptoms that are tolerable, with healthy or almost healthy mucosa
109 and a lack of need for systemic medication [9]. The Global Allergy and Asthma European
110 Network (GALEN) consortium was created in 2004 to increase interaction between European
111 research and clinical institutions, and to improve allergy and asthma research [6]. Since large
112 cross-sectional studies of CRS are lacking, we set up a large rhinosinusitis cohort study within
113 the GALEN consortium to identify inflammatory endotypes, the natural course of the disease,
114 and its impact on HRQoL in CRS patients.

115 The main objectives of the cohort were: 1) to describe the characteristics of the GALEN
116 rhinosinusitis cohort and provide detailed information on CRS patients and their
117 differentiating criteria; 2) to identify inflammatory endotypes and clinical phenotypes; 3) to
118 determine the natural course of the disease, including clinical characteristics and patient-

reported outcomes; and 4) to evaluate the impact of CRS on HRQoL in affected patients compared with controls, population norms for HRQoL, and the variation in HRQoL in different CRS phenotypes. This paper is a methodological overview of the GALEN rhinosinusitis cohort.

Materials and methods

Study design and setting

This multicentre cross-sectional case-control study was carried out by the GALEN Rhinosinusitis Cohort group (principal investigator, C. Bachert) within the framework of the European FP6 research initiative.

The cohort was set up for patients presenting in outpatient ear, nose and throat (ENT) clinics at nine University centres (Ghent, Leuven, Amsterdam, Barcelona, London, Berlin, Helsinki, Lodz, and Stockholm) in eight European countries (Belgium, Netherlands, Spain, UK, Germany, Finland, Poland, and Sweden). The protocol was approved by each participating centre's ethics committee, and patients signed written informed consent prior to recruitment between 25 April 2007 and 7 December 2009.

Participants

Adult CRS patients aged 18–60 years conforming to the EPOS 2007 [27] diagnostic criteria for CRS were recruited at the participating centres. Patients listed for inferior turbinate surgery without a history or symptoms of CRS or other chronic sinus diseases (irrespective of their allergy status) were included as unmatched control subjects (reference group). CRS patients who had had an exacerbation of allergic rhinitis in the past 2 weeks, or who had ever had functional endoscopic sinonasal surgery (FESS), were excluded from the study. The reference group patients were admitted to a tertiary centre and, although they did not report any medical history or have any symptoms of CRS, these patients may have nasal symptoms and a disease burden that are higher than in the healthy population. Detailed inclusion and exclusion criteria are provided in Supplementary Table 1.

Participant-reported and investigator-assessed data

The GALEN Rhinosinusitis Cohort study included participant-reported data (including patient-reported outcomes), investigator-reported data, and tissue samples for biomarker analyses. Information was collected in English, on paper-based forms. Validated local translations were used when required. The pseudonymized data were then entered into Microsoft© Excel spreadsheets and securely transferred to the Upper Airways Research Laboratory (URL) at Ghent University, Ghent, Belgium. The data were collected at URL Ghent and merged into a single file for analysis.

Participant-reported sociodemographics

The sociodemographic data collected included date of birth, gender, ethnicity, and place of work. A detailed cigarette smoking history (including information on house and workplace exposure to cigarette smoke) was collected. Details on alcohol consumption, and whether it worsened rhinosinusitis symptoms, were also collected. Environmental exposure to vehicular pollution, gas, dust, fumes, air conditioning, extremes of temperatures, and allergens were reported, in addition to the location of residence (city, semi-rural or rural).

Participant-reported disease characteristics

Detailed, self-reported information on symptoms and diagnosis was collected. Patients reported the year of their first sinus complaint, including the specialty of the diagnosing doctor. The participants also reported how their sinus problems began (headache, loss of smell, common cold, frequent episodes of acute sinusitis, or no specific medical history at the start of the problem). This list was developed based on expert input.

The participants were provided with the list of main CRS symptoms (blocked nose, facial pain/pressure, runny nose, loss of smell, mucus in throat, headache, and episodes of acute rhinosinusitis), which they then ranked chronologically based on when they noticed the symptoms. In addition, the participants also scored the duration (in months) and frequency (in

the last month) of these symptoms. The colour of nasal secretions (watery and colourless or thick and coloured) was also reported.

Participants reported general disease severity (overall rhinosinusitis) along with the severity of 10 symptoms (blocked nose, loss of smell, runny nose, sneezing, headache, facial pain/pressure, post-nasal drip, itchy nose, itchy ears, and itchy throat) and episodes of acute rhinosinusitis through a Visual Analogue Scale (VAS; 0–10 cm) that can measure both disease and individual symptom severity [27]. HRQoL was evaluated through the generic HRQoL scale, the Short Form-36 (SF-36) [28–31], and a disease-specific HRQoL scale, the Rhinosinusitis Outcome Measure-31 (RSOM-31) questionnaire [32, 33].

The details of previous medical and surgical treatments were recorded based on participant recall, as history of FESS was an exclusion criterion. In addition, current medications (type, dose, start/end date/if ongoing) and planned surgery, in those for whom it was indicated for the sinus condition, were also recorded.

Investigator-assessed patient and disease characteristics

The reporting of investigator-recorded patient characteristics and a lung function test (spirometry) for each participant were performed by a specialist. The allergic status of the patient was assessed by medical history and then confirmed by skin prick test using the pan-European allergen panel. In some participants, based on the investigator's decisions, a blood assay (radioallergosorbent test) or allergen provocation was undertaken. Medical history of allergic comorbidities was recorded for: 1) allergic rhinitis, including its classification based on Allergic Rhinitis and its Impact on Asthma guidelines (duration: intermittent, persistent; severity: mild, moderate-severe); 2) drug allergy or intolerance by type (penicillin, aspirin/other anti-inflammatory drugs, other); 3) eczema, including diagnosis year, whether ongoing, and current medication; 4) food allergy; 5) contact allergy; 6) urticaria; and 7) allergic bronchopulmonary aspergillosis.

Detailed medical history for lower respiratory conditions was collected for: 1) asthma, 2) chronic obstructive pulmonary disease (COPD), and 3) recent (within ≤ 3 weeks) bronchial infection.

Comorbid history of autoimmune diseases, diabetes, cystic fibrosis, ciliary dyskinesia, upper or lower gastrointestinal tract or other recurrent infections, and throat/voice complaints were also recorded.

Endoscopic examination

Enrolled patients underwent nasal endoscopy by an ENT or allergy specialist at their respective study centre, and the following quantitative or qualitative assessments were performed: nasal polyp score (NPS) were scored on a scale of 0–3 for each nostril (0, absence of polyps; 1, polyp[s] only in middle meatus; 2, polyps beyond the middle meatus not blocking the nose completely; and 3, polyps completely obstructing the nose), leading to a total score range of 0–6 for both nostrils.

CT scan of the paranasal sinuses

If the participant had an available computerized tomography (CT) scan of the paranasal sinuses not older than 12 months at the time of recruitment, it was scored by an ENT specialist. The scoring was based on the Lund–Mackay (LMK) scoring system [34]. In LMK scoring, the sinuses (maxillary, anterior/posterior ethmoid, sphenoid, and frontal) were each scored on a scale of 0–2 opacification (0, normal; 1, partial opacification; 2, total opacification). The ostiomeatal complex was scored on a two-point scale of 0 and 2 (0, not occluded; 2, occluded). The scores on each side ranged from 0 (complete translucency of all sinuses) to 12 (complete opacity of all sinuses), leading to a total LMK score of 24 for both sides.

Biomarker collection and assay

The tissue was analysed for interleukin (IL)-5, interferon (IFN)-γ, IL-17A, tumour-necrosis factor (TNF)-α, IL-22, IL-1b, IL-6, IL-8, eosinophilic cationic protein, myeloperoxidase, transforming growth factor (TGF)-β1, immunoglobulin (Ig)E, *Staphylococcus aureus*-specific IgE, and albumin. The results of the measurements of these inflammatory biomarkers have been published previously [6].

Serum/blood samples, nasal secretions, and nasal mucosal tissues were also collected.

Statistical methods

CRS and reference group patients were planned to be recruited at a ratio of 4:1, and each participating centre had a target of 100 CRS and 25 reference group participants. We analysed the CRSwNP, CRSsNP, and reference groups for descriptive comparison. Qualitative variables are summarised by counts and percentages; quantitative variables are summarised by mean, median, range, and standard deviation, and with the number of observations for each variable calculated. The denominator for percentages of patients is the total number of observations (N).

Means or proportions were tested for differences between CRSwNP vs reference group and CRSsNP vs reference group. Tests were two-sided, with a global type I error α of 5%. Qualitative and quantitative variables were compared using a permutation $\chi 2$ test.

Study participants with fewer than two completed variables were excluded from the analyses. The analyses used observed data. No data imputation was done. The statistical programmes used for the analyses include R and TANAGRA [35, 36].

Results

Participants

In total, 935 patients were recruited in random order from the nine participating centres at the outpatient ENT clinics. The flow chart (Figure 1) provides a description of the patients recruited and the sample sizes for analysis. 869 patients were included in the analyses. Table 1 provides a description of recruitment by centre and country.

Sociodemographic data

A total of 869 participants were eligible for analysis. Among these participants, 237 (27.3%) were classified as CRSsNP, 445 (51.2%) as CRSwNP, and 187 (21.5%) as references. The mean age was 40.6 years (range 16–76), 46.8 years (range 16–74), and 34.3 years (range 15–69) for CRSsNP, CRSwNP, and the reference group, respectively (Table 2). There were more males (55.0%; n/N: 432/786) than females in the study (Table 2); most participants were Caucasian (95.5%; 746/781), lived in a city (66.2%; 521/787) and were employed (95.6%; 738/772). Approximately one-third of the participants also reported an environmental exposure to gas, dust, fumes, air conditioning, extremes of temperatures, and allergens. Smoking (ever) was reported by 56.9% of the participants (448/787), out of which 21.2% were current smokers (31.2% of CRSsNP patients, 14.3% of CRSwNP patients and 21.3% of the reference group). Current alcohol consumption was reported by 41.9% of the participants (296/707). Mean [standard deviation (SD)] duration of symptoms was 11.7 (10.5) years, and mean (SD) duration of CRS diagnosis was 9.3 (10.2) years; over two-thirds of the participants were diagnosed by an ENT specialist and around one-third by a general physician.

Disease severity and HRQoL

The severity of the disease and of individual symptoms was determined by VAS. Both CRSsNP and CRSwNP patients had moderate-to-severe disease per EPOS criteria, with mean

VAS scores (SD) of 6.81 (2.34) and 6.40 (2.81), respectively (Table 2). CRS impaired HRQoL compared with the reference group, and its effect was observed with both the disease-specific (RSOM-31) and generic (SF-36 Version 1) HRQoL scales. The RSOM-31 severity scores were significantly higher for CRSsNP (mean [SD]: 59.14 [27.42]) patients vs the reference group (mean [SD]: 38.44 [30.51], $p < 0.00001$). Similarly, CRSwNP patients reported significantly greater severity (mean [SD]: 60.60 [29.70]) vs the reference group (mean [SD]: 38.44 [30.51]; $p < 0.00001$), indicating that CRS negatively affects patient HRQoL. These results on the impact on HRQoL in CRS patients were also observed in the SF-36 generic HRQoL scale, in which both CRSsNP and CRSwNP patients had significantly worse physical ($p < 0.00001$) and mental health ($p = 0.001$) compared with the reference group (Table 2).

Comorbidities

Asthma was one of the most frequent comorbidities reported by CRS patients. In this cohort, 20.2% of CRSsNP (44/218) and 49.6% of CRSwNP (173/349) patients reported asthma, compared with 13.6% of reference group patients (20/147; $p < 0.0001$ for CRSwNP vs reference group; Figure 2). The reported prevalence of asthma in the EU is 8.2% in adults [38].

The mean ages of asthma onset were 25.6, 34.0, and 23.9 years for CRSsNP, CRSwNP and reference group patients, respectively; 73.0%, 91.9% and 66.7% of CRSsNP (27/37), CRSwNP (113/123) and reference group patients (12/18) had late-onset asthma (after age 12 years), respectively [38]. (Figure 3). This difference was statistically significant only for CRSwNP patients compared with the reference group ($p = 0.007$), though not for CRSsNP patients ($p = 0.754$).

Nearly half (49.5% of CRSsNP [109/220] and 46.8% of CRSwNP [162/346]) of CRS patients reported being atopic, compared with approximately one-third of reference group patients (35.8%; [54/151]). These differences were statistically significant ($p = 0.006$ and $p = 0.018$ for

CRSsNP and CRSwNP vs the reference group, respectively). Allergic rhinitis was reported by approximately two-thirds of the participants. Eczema was reported by 17.5%, 16.5%, and 9.0% of CRSsNP (38/217), CRSwNP (57/345), and reference group patients, respectively (13/145; p = 0.033 for both CRS patient groups vs reference group).

Drug allergy (IgE-mediated) was almost twice as common in CRSsNP (30.6% [33/108]) and CRSwNP (38.2% [60/157]) patients than in the reference group (16.3% [8/49]; p = 0.054, p = 0.004 for CRSsNP and CRSwNP vs reference group, respectively). Among patients with a drug allergy, 51.5% of CRSsNP and 22.0% of CRSwNP patients reported a penicillin allergy, compared with 42.9% of the reference group (p = 0.532 and p = 0.43 respectively). Food allergy was reported by 18.1%, 13.3% and 12.2% in CRSsNP (19/105), CRSwNP (20/150) and reference group patients (6/49), respectively.

The proportion of patients reporting an aspirin or other NSAID hypersensitivity among patients with drug allergy was 9.1% for CRSsNP and 55.9% for CRSwNP patients vs 28.6% for reference group (p = 0.204 and p = 0.240 for CRSsNP and CRSwNP vs reference group respectively). The details of all comorbidities reported by the cohort are shown in Figure 2.

Objective disease assessment (Spirometry/NPS/LMK score)

Mean (SD) % predicted forced expiratory volume in 1 second (FEV1) values were 86.7% (17.27) for CRSsNP (77 total observations), 88.0% (17.27) for CRSwNP (204 total observations) and 90.3% (16.27) for the reference group (37 total observations) (p = 0.596 CRS vs control), irrespective of their asthma comorbidity. FEV1/forced vital capacity (FVC) ratios were < 80% in 43.4% of CRSsNP (33/76) and 63.3% of CRSwNP (136/215) patients, compared with 39.5% of the reference group (15/38; p = 0.836 and p = 0.006 for CRSsNP and CRSwNP vs reference group respectively).

Sinus involvement, as assessed by LMK CT scan scoring, was (mean [SD]) 8.28 (5.12) in

CRSsNP patients (n = 187) vs 1.16 (2.84) for the reference group (n = 31) ($p < 0.0001$). For CRSwNP patients (n = 298), the mean LMK score (SD) was 13.95 (5.52), which was also significantly different from the reference group ($p < 0.0001$). 58.3% of CRSsNP patients had an LMK score of ≥ 6 compared with 90.0% of CRSwNP patients. The distribution of LMK scores by sinus involvement is presented in Figure 4.

The NPS was assessed only in CRSwNP patients (n = 332), and the mean score (SD) was 3.07 (1.40) out of a maximum possible bilateral score of 6.

Medical and surgical treatment patterns

The proportion of patients who reported ever having received medical treatment for their sinus condition was 80.6% for CRSsNP (175/217) and 96.2% for CRSwNP (330/343) patients compared with 9.2% (13/141) for the reference group ($p < 0.00001$ for both CRSsNP and CRSwNP vs reference group; Figure 5). Intranasal corticosteroids (ICS) were the most frequently used medication, reported by 82.5% of the total cohort (396/480) and by 68.9% (111/161), 90.4% (274/303), and 68.8% (11/16) of CRSsNP, CRSwNP, and reference groups, respectively ($p = 0.018$ for CRSwNP vs reference group; Figure 5). Antibiotics were the second most used medication in the cohort (59.4%; 278/468), and use was significantly higher in CRSsNP patients vs reference group (70.4% [119/169] vs 20.0% [3/15]; $p < 0.00001$) than in CRSwNP patients vs reference group (54.9% [156/284] vs 20.0% [3/15]; $p = 0.015$; Figure 5). The third most frequent medication reported, oral corticosteroids (OCS; 46.2%; [212/459]), was reported by 23.5% [38/162], 61.3% [173/282], and 6.7% [1/15] of CRSsNP, CRSwNP and reference group participants, respectively. These differences were significant only for CRSwNP patients ($p = 0.196$ for CRSsNP and $p < 0.00001$ for CRSwNP vs reference group respectively; Figure 5). Antihistamines were used by 21.3% [35/164] of CRSsNP patients, 33.6% [89/265] of CRSwNP patients, and 20.0% [3/15] of reference group participants (Figure 5). Painkillers were used by a significantly higher proportion of CRSsNP

(40.1% [65/162], p = 0.010) than CRSwNP (27.6% [70/254], p = 0.123) patients vs reference group (6.7% [1/15]) (Figure 5).

Before the scheduled visit, 22.7% [49/216] of CRSsNP and 45.9% [155/338] of CRSwNP patients underwent sinonasal surgery. A revision sinonasal surgery was reported by 52.2% [23/44] of CRSsNP patients and 59.2% [81/137] of CRSwNP patients. Among the total population, 0.5% [1/187] of the reference group, 2.5% [6/237] of CRSsNP patients and 7.2% [32/445] of CRSwNP patients had had four or more sinus surgeries (Table 3).

Discussion

Currently, two CRS phenotypes can be distinguished – CRSsNP and CRSwNP. Several studies have previously attempted to characterise CRSwNP and CRSsNP patients based on inflammatory endotypes, microbiological profiles, allergy and comorbid conditions, symptoms, and HRQoL. More recently, using an extensive genealogical database linked to medical records, one large population-based study has attempted to characterise CRSwNP and CRSsNP based on the genetic- and/or environment-associated risk of carrying the same diagnosis in relatives and spouses of patients with these conditions [39]. However, these studies were conducted in relatively small numbers of patients, and their diagnostic criteria for CRS were not consistent. Other studies have included larger numbers of CRS patients. Hopkins et al. studied more than 3000 CRS patients. All included patients were undergoing sinonasal surgery for both CRSwNP and CRSsNP and were followed up for 5 years using the Sino-Nasal Outcome Test (SNOT-22) as the principal outcome measure. The studies demonstrated that sinonasal surgery is safe and effective in reducing the symptoms associated with CRS [40, 41].

The GALEN rhinosinusitis cohort allows for evaluation of multiple outcomes for CRS patients (including sociodemographic, patient-reported, physician-assessed, and objective scores) in addition to inflammatory endotypes.

The present paper reports a methodological overview of the GALEN rhinosinusitis cohort. This study provides detailed information on the impact of CRS on HRQoL, incidence of comorbidities, objective disease measures, and medical and surgical treatment patterns.

The average patients in this study had moderate-to-severe CRS and were symptomatic for more than a decade, alluding to the chronicity of the disease. There was a significant impact of CRS on HRQoL, demonstrated both by the high scores on the disease-specific RSOM-31 and the significantly higher burden compared with the reference group based on SF-36. SF-36 also showed an adverse impact of CRS on both the mental and physical health of patients.

401 Comorbidities were also frequently seen in this cohort compared with the reference group,
402 and nearly half of CRS patients suffered from a respiratory allergy. More CRSwNP patients
403 reported an aspirin or other NSAID hypersensitivity compared with CRSsNP patients and the
404 reference group.

405 Asthma was more frequent in CRS patients compared with the reference group. The
406 difference was statistically significant only for CRSwNP patients. A higher proportion of CRS
407 patients had impaired lung function, as demonstrated by an FEV1/FVC ratio of <80%,
408 compared with the reference group. This proportion was higher than those reporting asthma,
409 suggesting a probable under-diagnosis of asthma. CRS patients also had a significantly higher
410 prevalence of eczema, drug allergy, and COPD compared with the reference group.

411 The most common treatments for both CRSsNP and CRSwNP were ICS, antibiotics and oral
412 steroids. In comparison with the reference group, CRS patients are more frequently treated
413 with antibiotics. Significant differences were observed between CRSsNP and CRSwNP
414 patients compared with the reference group in the use of painkillers and OCS, respectively.

415 Surgery is a frequent treatment option, and approximately a quarter of CRSsNP and half of
416 CRSwNP patients reported a previous operation. Among patients with previous surgery,
417 59.2% of the CRSwNP and 52.2% of the CRSsNP group had at least one additional surgery.
418 However, the type and extent of surgery performed was not evaluated in this study. Fifty-three
419 percent of patients with CRSsNP and 31.9% of CRSwNP patients had a surgery planned at
420 baseline visit.

421 Tomassen and colleagues [6] reported the identification of inflammatory endotypes of CRS,
422 using a phenotype-free approach, in a subset of the GALEN sinusitis cohort. These analyses
423 were performed on 173 CRS patients and 89 control patients, for whom sufficient tissue for
424 analysis was available. Patients were grouped into 10 inflammatory endotype clusters based
425 on immune markers. These were then compared post hoc with selected phenotype parameters,

426 such as NP prevalence and asthma comorbidity. Three clusters were composed exclusively of
427 CRSsNP without asthma, while three were composed exclusively of CRSwNP with a high
428 proportion of asthma comorbidity.

429 The GALEN rhinosinusitis cohort is not an epidemiological study, and the patients were
430 included in order of random presentation at the study centres. Patient distribution does not
431 reflect distribution of the disease in the general population, but rather the specific recruitment
432 patterns of the respective clinics. Although the inclusion criteria specified inclusion of
433 patients aged > 18–60 years, 7/869 (0.8%) patients < 18 and 52/869 (6.0%) patients > 60 were
434 also recruited and included in these analyses. The study centres were large tertiary ones,
435 which may have led to an inclusion bias towards more severe cases and patients with a higher
436 disease burden. It is also possible that more such patients were willing to participate. The
437 reference group patients were not healthy, and although they did not report any medical
438 history or have any symptoms of CRS, these patients may have had a nasal and asthma
439 symptom load that is higher than in the healthy population. Moreover, since these patients had
440 other ENT conditions, they had VAS severity and RSOM scores that were higher than in the
441 healthy population; half of the control group was scheduled for conchectomy/turbinectomy
442 (data not shown).

443 The data were based on recall, and therefore may suffer from a recall bias. However, as
444 patients and physicians completed their respective sub-questionnaires concurrently, this
445 decreased the risks of bias and large variation in the clinical evaluation of the patients.

446 The GALEN rhinosinusitis cohort allows for the possibility of studying CRS and its main
447 phenotypes, being one of the largest CRS databases in Europe, and includes data on
448 sociodemographic variables; environmental exposure; symptom and disease chronology;
449 patient-reported outcomes, including HRQoL; physician-assessed data, including
450 comorbidities; and objective measures such as NPS, CT scans, and lung function. In addition,

451 the cohort is also a rich source of multiple biomarkers as we move towards precision
452 medicine.

453

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458

459 Authorship contributions

460 AK: Reviewed and interpreted results, and provided direction for manuscript development
461 and critical feedback. GV and CB: Contributed to protocol development, acquired data,
462 reviewed and interpreted results, and provided direction for manuscript development and
463 critical feedback. TMTH: Performed statistical analysis of data, reviewed and interpreted
464 results, and provided direction for manuscript development and critical feedback. VNJ, LM,
465 PT, TVZ, L-OC, JA, HO, UF-R, MLK, AO-Z, GH, NDR, CVD, JM, PWH, VH, ET, GS, VL,
466 and WF: Acquired data, reviewed and interpreted results, and provided direction for
467 manuscript development and critical feedback.

468

469 Conflict of interest

470 Khan A: Sanofi employee, may hold stock and/or stock options in the company.

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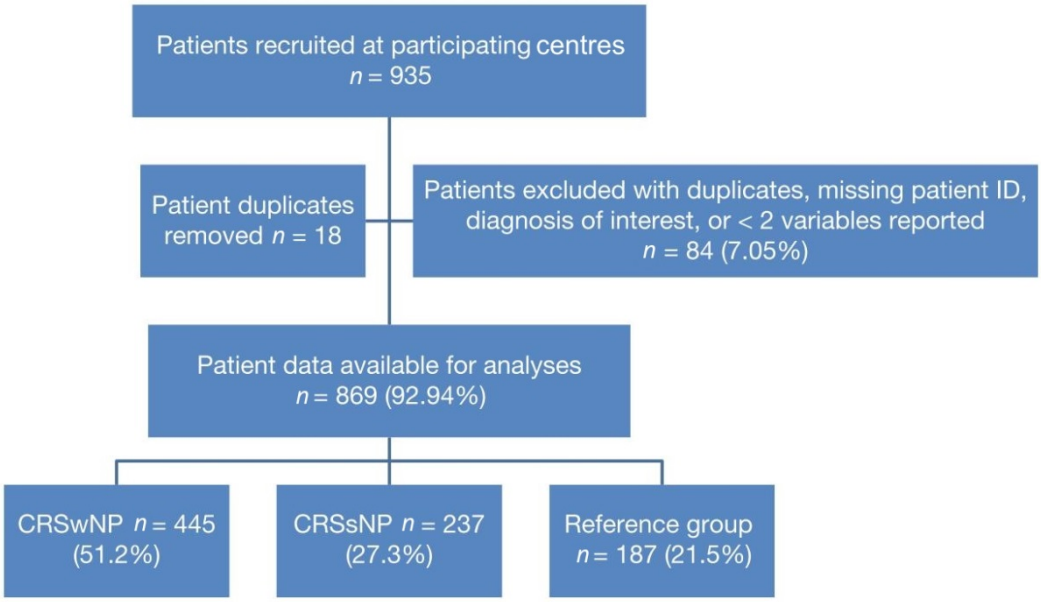
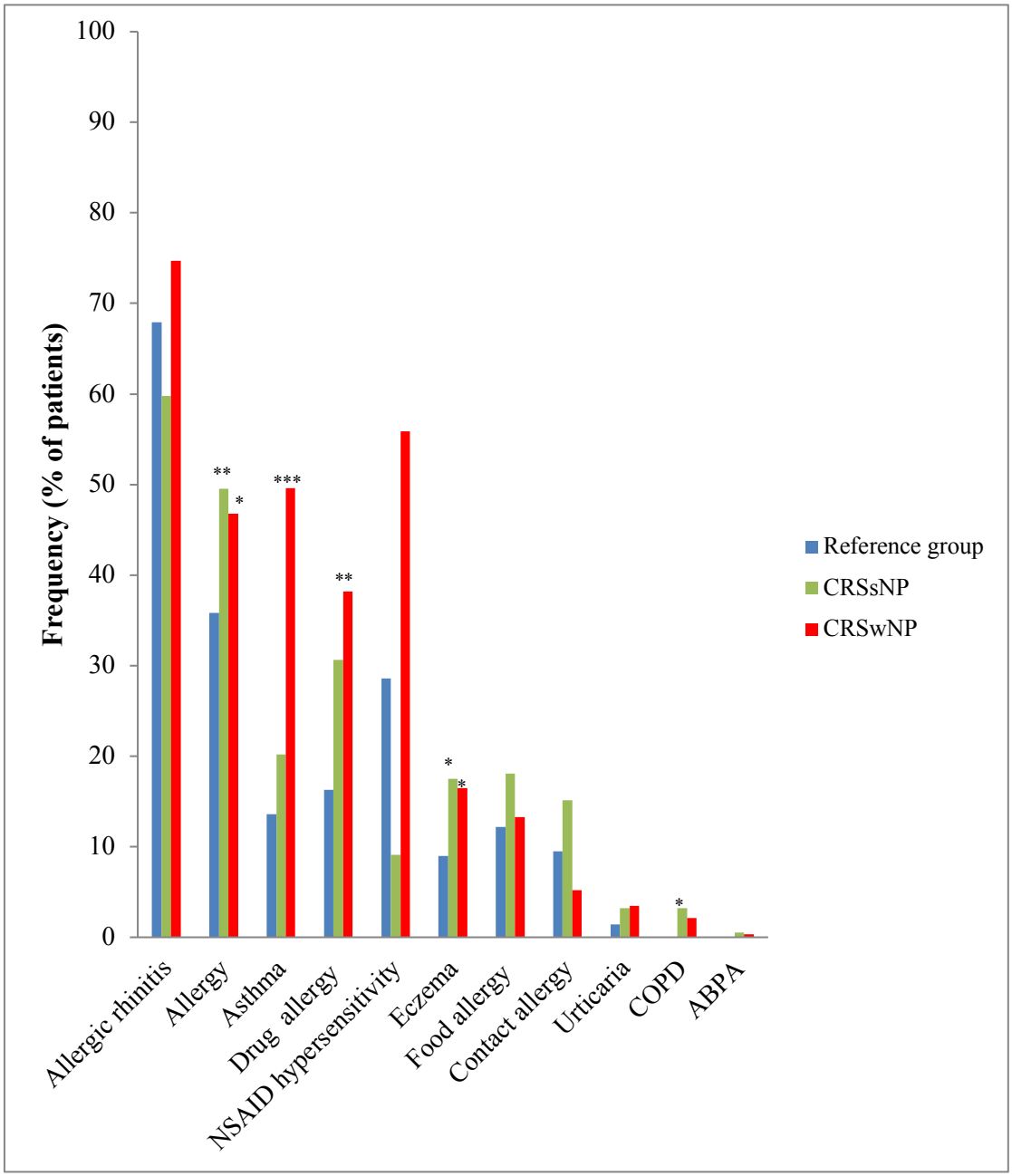
Figures

Figure 1. GALEN Rhinosinusitis Cohort. Patient disposition.



622 Figure 2. GALEN Rhinosinusitis Cohort. Distribution of comorbidities among

623 patients with drug allergy.



624

625 *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; compared with the reference group. ABPA,

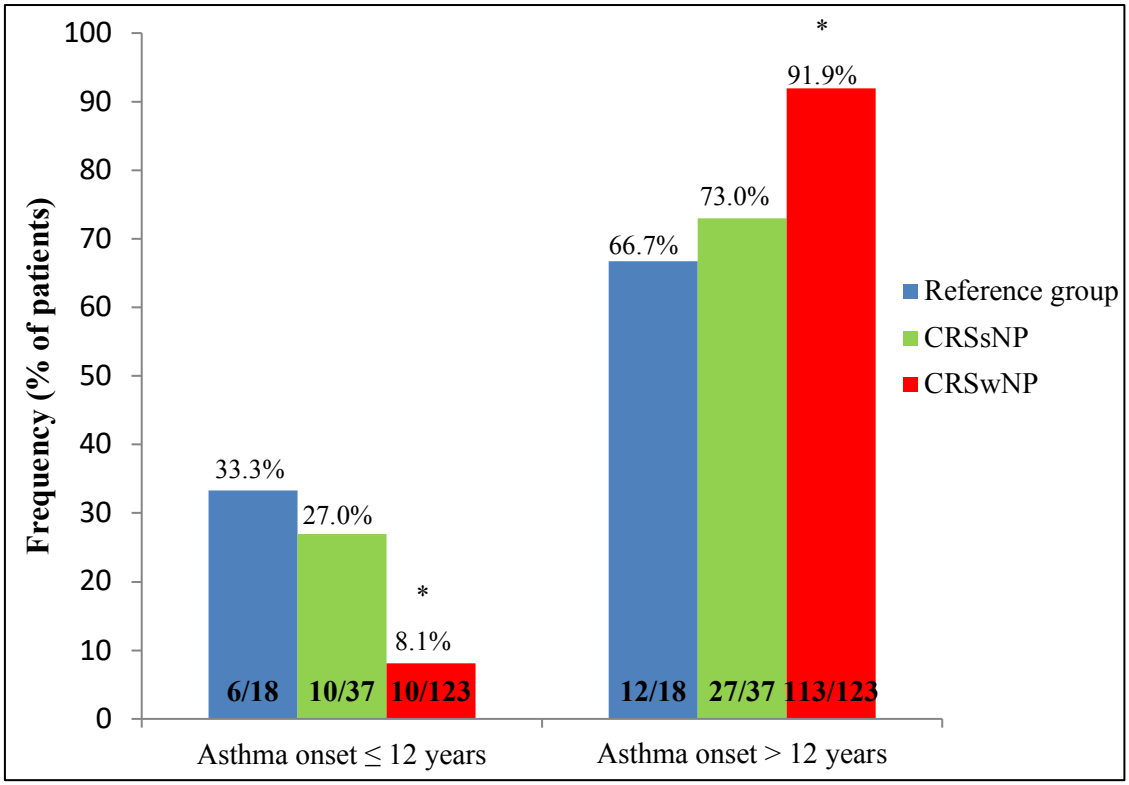
626 allergic bronchopulmonary aspergillosis; COPD, chronic obstructive pulmonary

627 disease.

628

629 Figure 3. GALEN Rhinosinusitis Cohort. Percentage of patients with asthma onset

630 by age group.



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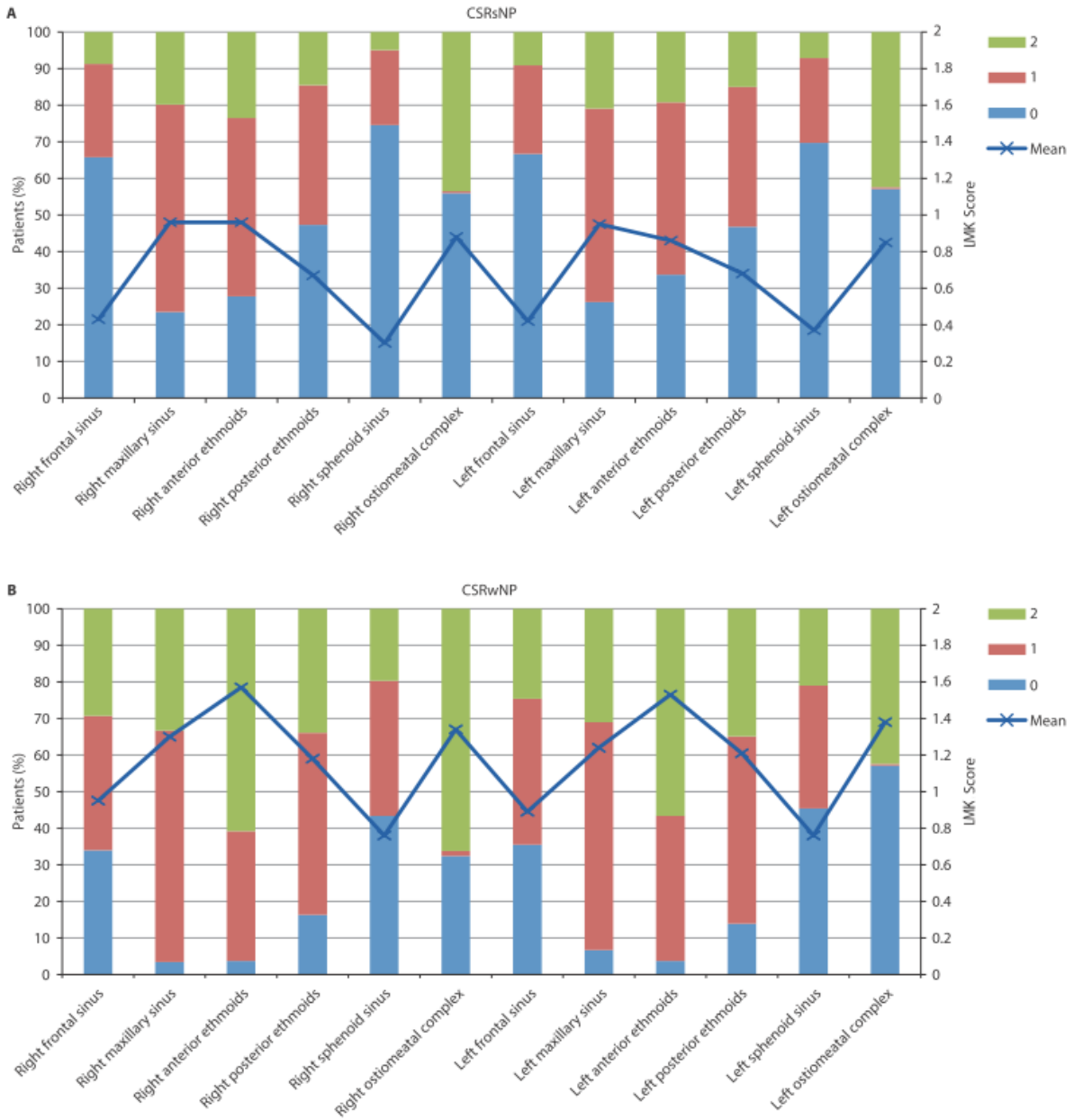
632 *p = 0.007 compared with the reference group.

633

634 Figure 4. Distribution of the LMK scores in (A) CRSsNP patients and (B) CRSwNP

635 patients.



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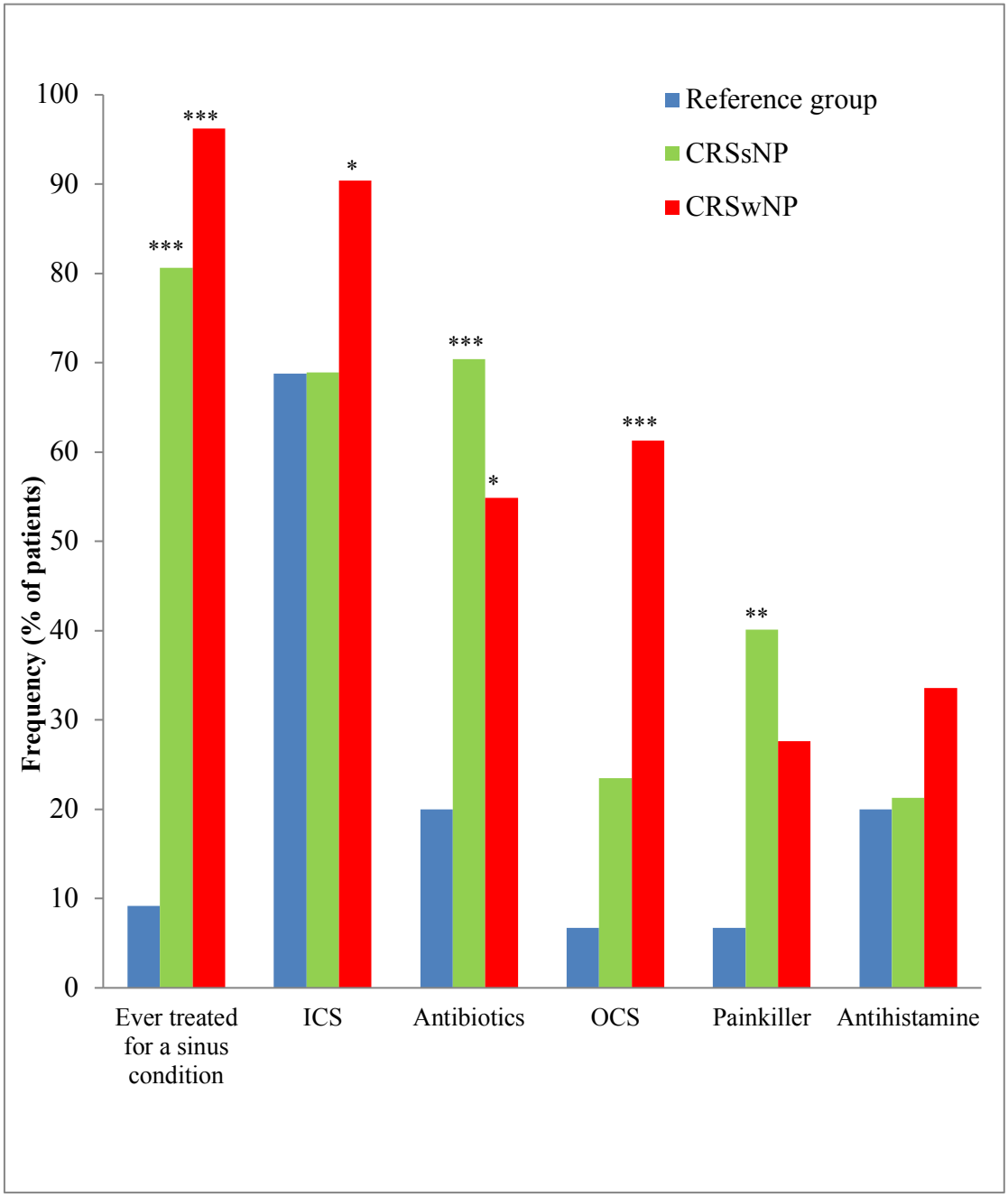
638 Figure 5. GALEN Rhinosinusitis Cohort. Treatment patterns.



639

640 *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.00001 compared with the reference group.

641

Tables

Table 1. GALEN Rhinosinusitis Cohort. Recruitment by centre and country.

Centre name (country)	Country	Reference group (*n* = 187), analysed patients, n (%)	CRSsNP (*n* = 237), analysed patients, n (%)	CRSwNP (*n* = 445), analysed patients, n (%)	All (*n* = 869), analysed patients, n (%)
Royal National Throat, Nose and Ear Hospital, London	United Kingdom	5 (2.7)	1 (0.4)	6 (1.3)	12 (1.4)
University Hospitals Leuven	Belgium	17 (9.1)	16 (6.8)	8 (1.8)	41 (4.7)
Karolinska Institutet, Stockholm	Sweden	18 (9.6)	28 (11.8)	42 (9.4)	88 (10.1)
Helsinki University Central Hospital	Finland	31 (16.6)	0	59 (13.3)	90 (10.4)
Academic Medical Centre, Amsterdam	Netherlands	17 (9.1)	24 (10.1)	61 (13.7)	102 (11.7)
Hospital Clínic–IDIBAPS, Barcelona	Spain	0	8 (3.4)	100 (22.5)	108 (12.4)
Medical Universities of Łódź and Kraków	Poland	28 (15)	16 (6.8)	95 (21.3)	139 (16)

Ghent University Hospital	Belgium	43 (23)	48 (20.3)	50 (11.2)	141 (16.2)
Charité – Universitätsmedizin Berlin	Germany	28 (15)	96 (40.5)	24 (5.4)	148 (17)

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

Table 2. GALEN Rhinosinusitis Cohort. Demographics and baseline characteristics.

	Reference group n = 187 (21.5% of analysed patients)	CRSsNP n = 237 (27.3% of analysed patients)	CRSwNP n = 445 (51.2% of analysed patients)	All n = 869 (100% of analysed patients)
Age, number of observations	180	228	380	788
Years, mean (SD)	34.3 (12.6)	40.6 (12.6)	46.8 (11.2)	42.1 (12.9)
Years, median	32	41	48	43
Range	15:69	16:76	17:74	15:76
Gender, number of observations	179	228	379	786
Male, n (%)	98 (54.7)	112 (49.0)	222 (58.6)	432 (55)
Duration of symptoms, number of observations, years	14	202	339	555
Years, mean (SD)	12.1 (10)	9.8 (10.5)	12.8 (10.5)	11.7 (10.5)
Years, median	8.5	6	10	9
Range	2:38	0:57	0:47	0:57
Diagnosed since, number of observations, years	9	208	320	537

Years, mean (SD)	12.1 (12.2)	7.3 (9.9)	10.5 (10.1)	9.3 (10.2)
Years, median	8	3	8	6
Range	1:38	0:57	0:50	0:57
VAS rhinosinusitis, n (%)	152 (80.4)	220 (92.8)	341 (76.6)	713 (82.0)
Score, Mean (SD)	3.93 (3.55)	6.81 (2.34)***	6.40 (2.81)***	6.0 (3.05)
SF-36 physical (PCS), n (%)	170 (89.9)	219 (92.4)	350 (78.7)	744 (85.6)
Score, Mean (SD)	50.43 (8.45)	42.67 (9.67)***	45.68 (9.45)***	45.88 (9.70)
SF-36 mental (MCS), n (%)	170 (89.9)	219 (92.4)	355 (79.8)	744 (85.6)
Score, Mean (SD)	50.03 (9.73)	46.7 (10.69)**	46.86 (11.39)*	47.54 (10.88)
RSOM-31 (severity), n (%)	157 (84.0)	217 (91.6)	336 (75.5)	710 (81.7)
Score, Mean (SD)	38.44 (30.51)	59.14 (27.42)***	60.60 (29.70)*	55.25 (30.52)
RSOM-31 (importance), n (%)	122 (65.2)	186 (78.5)	270 (60.7)	578 (66.5)
Score, Mean (SD)	58.66 (25.36)	71.07 (21.39)***	74.41 (22.33)***	70.01 (30.52)

* $p = 0.002$; ** $p = 0.001$; *** $p < 0.00001$ compared with the reference group. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; RSOM-31, Rhinosinusitis Outcome Measure-31 questionnaire; SF-36, Short Form-36; VAS, Visual Analogue Scale.

Table 3. GALEN Rhinosinusitis Cohort. Number of previous surgeries.

Patients with previous surgery, n (%)	Reference group n = 187	CRSsNP n = 237	CRSwNP n = 445
1	4 (2.1)	21 (8.9)	56 (12.6)
2	1 (0.5)	11 (4.6)	29 (6.5)
3	0	6 (2.5)	20 (4.5)
4	1 (0.5)	6 (2.5)	32 (7.2)

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

Supplementary tables

Supplementary Table 1. Inclusion and exclusion criteria of the GALEN Rhinosinusitis Cohort.

Inclusion criteria	
For all subjects	1. The subject understands the study procedures and agrees to participate by signing the consent form. 2. The subject is male or female between 18 and 60 years of age. 3. Except for the diagnosis of CRS, subjects must be in good health, free of any clinically significant disease that would interfere with the study or procedures or compromise his/her safety.
Diagnosis of CRS (with or without nasal polyps, including fungal disease, cystic fibrosis) is based on the EPOS4 definition and all patients should have:	
	1. Inflammation of the nose and the paranasal sinuses characterised by two or more symptoms (one should always be a or b)
	a. Nasal congestion/obstruction/blockade
	b. Nasal discharge: anterior/posterior nasal drip
	c. Facial pain/pressure
	d. Reduction/loss of smell
	2. And either (one of the criteria below)
	a. Endoscopic signs

	− Nasal polyps
	− Mucopurulent discharge from the middle meatus
	− Oedema/mucosal obstruction primarily in the middle meatus
	3. And
	a. CT changes: mucosal changes within the ostiomeatal complex and/or paranasal sinuses
	b. Duration of the disease: > 12 weeks of symptoms
	c. No complete resolution of the symptoms
	NB: Patients with antrochoanal polyps were excluded.
Control	Control patients are patients undergoing nasal surgery such as septoplasty or septorhinoplasty, who have no medical history or symptoms of any form of CRS, nasal polyposis, cystic fibrosis or other chronic sinus disease. Trauma patients and patients undergoing transnasal approaches for hypophysectomy and surgery for exophthalmia could be included as controls as well. Patients with allergy (sensitisation and clinically relevant allergy) were allowed in the control group, and allergy tests were done and documented.
Exclusion criteria	
General exclusions	
	1. Patients with a recent acute exacerbation of rhinosinusitis (past 2 weeks) are not allowed to participate.
	2. The subject had former FESS, with removal of parts of the lateral nasal wall. Simple polypectomy, septal or inferior

	turbinate surgery is allowed.
	3. Women must not be pregnant or breastfeeding.
	4. The subject is a current or recent past abuser of alcohol or illicit drugs.
	5. The subject has a history of malignancy, is known to be positive for HIV, or has immunodeficiency or other states that are considered to interfere with study conduct or scientific interpretations.
	6. Subjects must not be known to have sarcoidosis.
	7. Subjects must not be known to have any type of vasculitis (including Wegener).
	8. Subjects must not be known to be positive to hepatitis B surface antigen or C antibodies.
	9. The subject cannot read or comprehend written material, or is, in the opinion of the investigator, for other reasons unlikely to understand and follow the study procedures.
	10. The subject is mentally or legally incapacitated preventing informed consent from being obtained.
	11. Medication wash-out is mandatory only in case of biopsy, for other patients it is optional (medication wash-out period: oral steroids 4 weeks; nasal steroids 4 weeks; anti-leukotrienes 2 weeks).
	12. Inhaled corticosteroids for asthma are permitted but should be documented in the questionnaires.

CRS, chronic rhinosinusitis; CT, computerized tomography; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; FESS, functional endoscopic sinus surgery; HIV, human immunodeficiency virus.