OPEN ACCESS

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*

Asif Khan[1,2,#], Griet Vandeplas[2,#], Thi Minh Thao Huynh[1], Vijay N. Joish[3,##], Leda P. Mannent[1], Peter Tomassen[2], Thibaut van Zele[2], Lars-Olaf Cardell[4], Julia Arebro[4], Heidi Olze[5], Ulrike Förster-Ruhrmann[5], Marek L. Kowalski[6], Agnieszka Olszewska-Ziąber[6], Gabriële Holtappels[2], Natalie De Ruyck[2], Cornelis van Drunen[7], Joaquim Mullol[8], Peter W. Hellings[9], Valérie Hox[9], Elina Toskala[10], Glenis Scadding[11], Valerie J. Lund[11], Wytske J. Fokkens[7], Claus Bachert[2,4]

[1] Sanofi, Chilly Mazarin, France

[2] Ghent University, Ghent, Belgium

[3] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

[4] CLINTEC, Karolinska Institutet, Stockholm, Sweden

[5] Charité-Universitätsmedizin, Berlin, Germany

[6] Medical University of Łódź, Łódź, Poland

[7] Academic Medical Center, Amsterdam, the Netherlands

[8] Hospital Clínic – IDIBAPS and Universitat de Barcelona, Barcelona, Spain

[9] University Hospitals Leuven, Leuven, Belgium

[10] Temple University School of Medicine, Philadelphia, PA, USA

[11] Royal National Throat, Nose and Ear Hospital, London, UK

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.

Methods: 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: cohort studies, cross-sectional studies, nasal polyps, rhinitis, sinusitis

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 ≥ 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 2 groups. However, patients with CRSwNP score more frequently and significantly higher on nasal symptoms such as rhinorrhoea, nasal congestion or obstruction, and olfactory deficits (the most discriminant symptom is loss of smell) compared with those with CRSsNP [8, 10], who more frequently report facial pain [11].

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

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

The main objectives of the cohort were: 1) to describe the characteristics of the GALEN rhinosinusitis cohort and provide detailed information on CRS patients and their differentiating criteria; 2) to identify inflammatory endotypes and clinical phenotypes; 3) to 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 9 University centres (Ghent, Leuven, Amsterdam, Barcelona, London, Berlin, Helsinki, Łódź, and Stockholm) in eight European countries (Belgium, the 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
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 decision, 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-
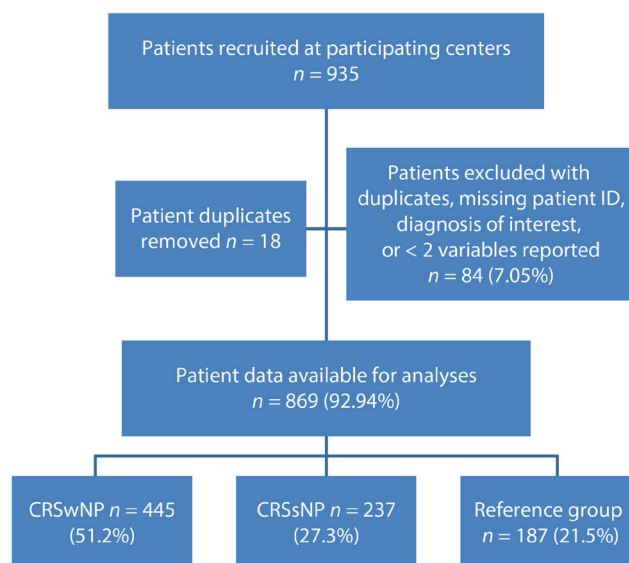

Figure 1. GALEN Rhinosinusitis Cohort. Patient disposition. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; GALEN, Global Allergy and Asthma European Network; ID, identification.

inflammatory drugs, or 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

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

Centre name	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	UK	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	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	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	Germany	28 (15)	96 (40.5)	24 (5.4)	148 (17)

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps. ; GALEN, Global Allergy and Asthma European Network.

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 2-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-1β, 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 2-sided, with a global type I error α of 5%. Qualitative and quantitative variables were compared using a permutation χ2 test.

Study participants with fewer than 2 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 9 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

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	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	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; ; GALEN, Global Allergy and Asthma European Network; RSOM-31, Rhinosinusitis Outcome Measure-31 questionnaire; SD, standard deviation; SF-36, Short Form-36; VAS, Visual Analogue Scale.

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 pa-
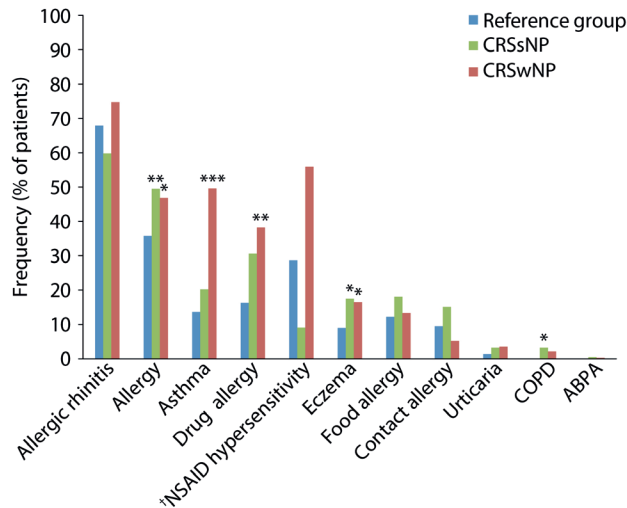
Figure 2. GALEN Rhinosinusitis Cohort. Distribution of comorbidities among CRSsNP and CRSwNP.

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; compared with the reference group. †Among patients with drug allergy. ABPA, allergic bronchopulmonary aspergillosis; COPD, chronic obstructive pulmonary disease ; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; GALEN, Global Allergy and Asthma European Network.

Figure 3. GALEN Rhinosinusitis Cohort. Percentage of patients with asthma onset by age group.

*p = 0.007 compared with the reference group. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; GALEN, Global Allergy and Asthma European Network.

tients 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 [37].

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),
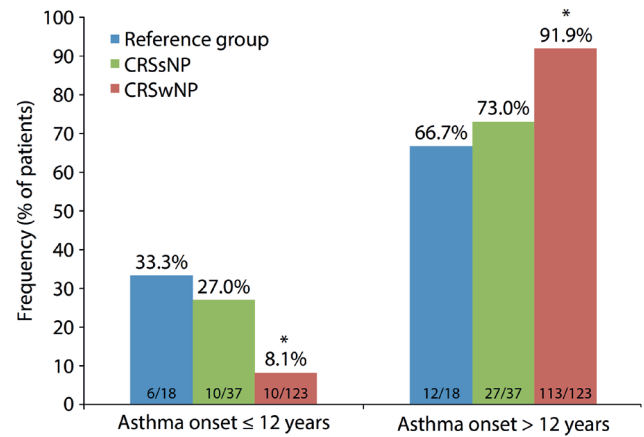
and reference group patients, respectively (13/145; p = 0.033 for both CRS patient groups vs reference group).

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).
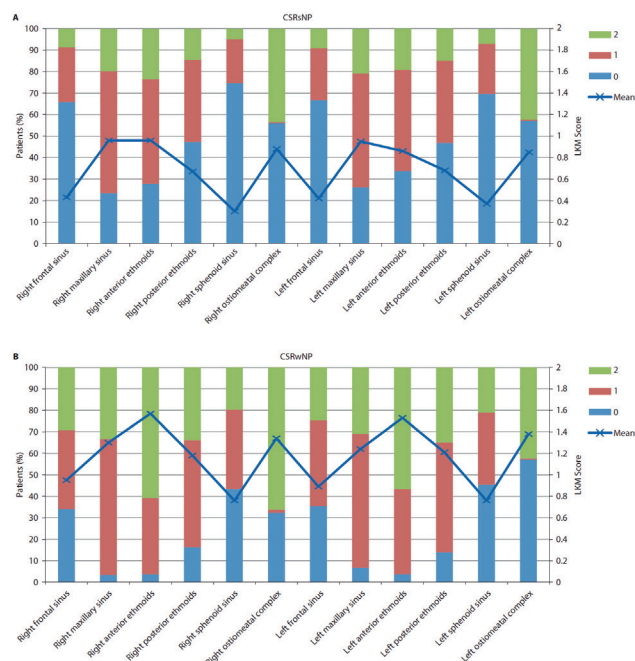
Figure 4. Distribution of the LMK scores in (A) CRSsNP patients and (B) CRSwNP patients. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; GALEN, Global Allergy and Asthma European Network.

Figure 5. GALEN Rhinosinusitis Cohort. Treatment patterns. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosi- nusitis with nasal polyps; GALEN, Global Allergy and Asthma European Network. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.00001 compared with the refer- ence group.

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 CRS- sNP (175/217) and 96.2% for CRSwNP (330/343) patients com- pared with 9.2% (13/141) for the reference group (p < 0.00001 for both CRSsNP and CRSwNP vs reference group; Figure 5). Intranasal corticosteroids (INCS) 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
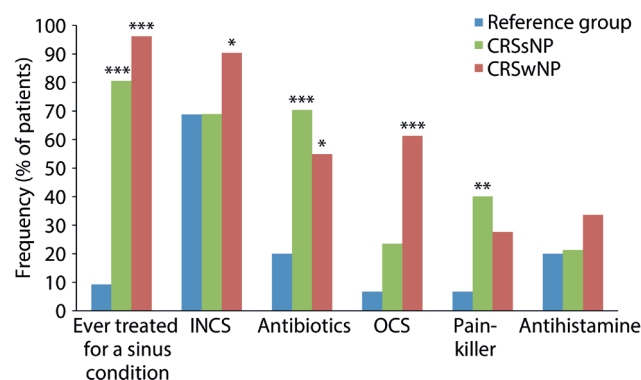
CRSwNP patients vs reference group (54.9% [156/284] vs 20.0% [3/15]; p = 0.015; Figure 5). The third most frequent medica- tion reported, oral corticosteroids (OCS; 46.2% [212/459]), was reported by 23.5% [38/162], 61.3% [173/282], and 6.7% [1/15] of CRSsNP, CRSwNP, and reference group participants, res- pectively. 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 partici- pants (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 CRS- sNP 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 pa- tients had had 4 or more sinus surgeries (Table 3).

Discussion
Currently, two CRS phenotypes can be distinguished – CRSsNP and CRSwNP. Several studies have previously attempted to char- acterise CRSwNP and CRSsNP patients based on inflammatory endotypes, microbiological profiles, allergy and comorbid condi- tions, 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

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 ; GALEN, Global Allergy and Asthma European Network.

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.

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

Asthma was more frequent in CRS patients compared with the reference group. The difference was statistically significant only for CRSwNP patients. A higher proportion of CRS patients had impaired lung function, as demonstrated by an FEV1/FVC ratio of < 80%, compared with the reference group. This proportion

was higher than those reporting asthma, suggesting a probable under-diagnosis of asthma. CRS patients also had a significantly higher prevalence of eczema, drug allergy, and COPD compared with the reference group.

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

Surgery is a frequent treatment option, and approximately a quarter of CRSsNP and half of CRSwNP patients reported a previous operation. Among patients with previous surgery, 59.2% of the CRSwNP and 52.2% of the CRSsNP group had at least one additional surgery. However, the type and extent of surgery performed was not evaluated in this study. 53% of patients with CRSsNP and 31.9% of CRSwNP patients had a surgery planned at baseline visit.

Tomassen and colleagues [6] reported the identification of inflammatory endotypes of CRS, using a phenotype-free approach, in a subset of the GALEN sinusitis cohort. These analyses were performed on 173 CRS patients and 89 control patients, for whom sufficient tissue for analysis was available. Patients were grouped into 10 inflammatory endotype clusters based on immune markers. These were then compared post hoc with selected phenotype parameters, such as NP prevalence and asthma comorbidity. Three clusters were composed exclusively of CRSsNP without asthma, while 3 were composed exclusively of CRSwNP with a high proportion of asthma comorbidity.

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

The data were based on recall, and therefore may suffer from a recall bias. However, as patients and physicians completed their

respective sub-questionnaires concurrently, this decreased the risks of bias and large variation in the clinical evaluation of the patients.

Conclusion

The GALEN rhinosinusitis cohort allows for the possibility of studying CRS and its main phenotypes, being one of the largest CRS databases in Europe, and includes data on sociodemographic variables; environmental exposure; symptom and disease chronology; patient-reported outcomes, including HRQoL; physician-assessed data, including comorbidities; and objective measures such as NPS, CT scans, and lung function. In addition, the cohort is also a rich source of multiple biomarkers as we move towards precision medicine.

Acknowledgements

Authorship contribution

AK: Reviewed and interpreted results, and provided direction for manuscript development and critical feedback. GV and CB: Contributed to protocol development, acquired data, reviewed and interpreted results, and provided direction for manuscript development and critical feedback. TMTH: Performed statistical analysis of data, reviewed and interpreted results, and provided direction for manuscript development and critical feedback. VNJ, LPM, PT, TvZ, L-OC, JA, HO, UF-R, MLK, AO-Z, GH, NDR, CvD, JM, PWH, VH, ET, GS, VJL, and WJF: Acquired data, reviewed and interpreted results, and provided direction for manuscript development and critical feedback.

Conflict of interest

AK: Sanofi employee, may hold stock and/or stock options in the company. TMTH: Sanofi employee, may hold stock and/or stock options in the company. VNJ: (Previously) Regeneron Pharmaceuticals, Inc. employee and shareholder. LPM: Sanofi employee, may hold stock and/or stock options in the company. UF-R: Novartis (received fee for lectures). CvD: Allergopharma, EU, FWO, GSK, NWO research grants. JM: ALK-Abelló, FAES, Genentech, GSK, MEDA Pharma, Menarini, MSD, Novartis, Sanofi-Genzyme, Regeneron Pharmaceuticals, Inc., UCB, Uriach Group and is, or has been, a member of national and international scientific advisory boards (consulting), received fees for lectures, and grants for research projects. ET: Allergan advisory board member. GS: ALK, GSK research grants; ALK, Astra Zeneca, Brittania Pharmaceuticals, Capnia, Church & Dwight, Circassia, Danone, GSK, MEDA, Merck, Mylan, MSD, Ono Pharmaceuticals, Oxford Therapeutics, Sanofi-Aventis, Shionogi, UCB, Uriach honoraria for articles, consulting, lectures/chairing and/or advisory boards; Bayer, GSK travel funding. VJL: Crucell, Johnson & Johnson advisory board member; GlaxoSmithKline, MEDA Pharma – research funding; MSD – paid lectureship. WJF: BioInspire, GSK, MEDA, Sanofi research grants; Rhinology, editor. CB: GSK, Novartis, Sanofi Principal Investigator.
GV, PT, TvZ, L-OC, JA, HO, MLK, AO-Z, GH, NDR, PH, VH: No conflicts of interest to disclose.

References

1. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA^{2}LEN study. Allergy 2011; 66: 1216-1223.
2. Hirsch AG, Stewart WF, Sundaresan AS, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy 2017; 72: 274-281.
3. Klossek JM, Neukirch F, Pribil C, et al. Prevalence of nasal polyposis in France: a cross-sectional, case–control study. Allergy 2005; 60: 233-237.
4. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol 1999; 28: 717-722.
5. Shi JB, Fu QL, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. Allergy 2015; 70: 533-539.
6. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol 2016; 137: 1449-1456.
7. Bachert C, Pawankar R, Zhang L, et al. ICON: chronic rhinosinusitis. World Allergy Organ J 2014; 7: 25.
8. Huvenne W, van Bruaene N, Zhang N, et al. Chronic rhinosinusitis with and without nasal polyps: what is the difference? Curr Allergy Asthma Rep 2009; 9: 213-220.
9. Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012; 23: 1-298.
10. Dietz de Loos DA, Hopkins C, Fokkens WJ. Symptoms in chronic rhinosinusitis with and without nasal polyps. Laryngoscope 2013; 123: 57-63.
11. DeConde AS, Mace JC, Ashby S, Smith TL, Orlandi RR, Alt JA. Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments. Int Forum Allergy Rhinol 2015; 5: 682-690.
12. Alobid I, Cardelus S, Benítez P, et al. Persistent asthma has an accumulative impact on the loss of smell in patients with nasal polyposis. Rhinology 2011; 49: 519-524.
13. Bachert C, Zhang N, Holtappels G, et al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. J Allergy Clin Immunol 2010; 126: 962-968.
14. Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. Int Forum Allergy Rhinol 2016; 6: 373-377.
15. Håkansson K, Bachert C, Konge L, et al. Airway inflammation in chronic rhinosinusitis with nasal polyps and asthma: the united airways concept further supported. PLoS One 2015; 10: e0127228.
16. Håkansson K, Thomsen SF, Konge L, Mortensen J, Backer V, von Buchwald C. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy 2014; 28: 383-387.
17. Bachert C, Zhang L, Gevaert P. Current and

future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. J Allergy Clin Immunol 2015; 136: 1431-1440.

18. Kowalski ML, Ptasinska A, Bienkiewicz B, Pawliczak R, DuBuske L. Differential effects of aspirin and misoprostol on 15-hydroxy-eicosatetraenoic acid generation by leukocytes from aspirin-sensitive asthmatic patients. J Allergy Clin Immunol 2003; 112: 505-512.

19. Batra PS, Tong L, Citardi MJ. Analysis of comorbidities and objective parameters in refractory chronic rhinosinusitis. Laryngoscope 2013; 123 suppl 7: S1-S11.

20. Sharma R, Lakhani R, Rimmer J, Hopkins C. Surgical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev 2014; 11: CD006990.

21. Mullol J, Picado C. Rhinosinusitis and nasal polyps in aspirin-exacerbated respiratory disease. Immunol Allergy Clin North Am 2013; 33: 163-176.

22. Barham HP, Osborn JL, Snidvongs K, Mrad N, Sacks R, Harvey RJ. Remodeling changes of the upper airway with chronic rhinosinusitis. Int Forum Allergy Rhinol 2015; 5: 565-572.

23. Kumar K, Shah A. Effect of nasal polyposis on nocturnal sleep disturbances, daytime sleepiness, and sleep specific quality of life disturbances in patients presenting with allergic rhinitis. Ann Allergy Asthma Immunol 2014; 113, A17.

24. Vaid L, Khanna S, Singh PP. Impact of nasal polyps on quality of life of chronic sinusitis patients. Indian J Otolaryngol Head Neck Surg 2007; 59: 136-141.

25. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. Int Forum Allergy Rhinol 2016; 6 suppl 1: S22-S209.

26. Hellings PW, Fokkens WJ, Akdis C, et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 2013; 68: 1-7.

27. Fokkens WJ, Lund V, Mullol J; European Position Paper on Rhinosinusitis and Nasal Polyps Group. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. Rhinology 2007; 45: 97-101.

28. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I: conceptual framework and item selection. Med Care 1992; 30: 473-483.

29. Ware JE Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995; 33 suppl 4: AS264-AS279.

30. Alobid I, Benítez P, Bernal-Sprekelsen M, et al. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. Allergy 2005; 60: 452-458.

31. Alobid I, Benítez P, Pujols L, et al. Severe nasal polyposis and its impact on quality of life. The effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology 2006; 44: 8-13.

32. Piccirillo JF, Edwards D, Haiduk A, Yonan C, Thawley SE. Psychometric and clinimetric validity of the 31-item Rhinosinusitis Outcome Measure (RSOM-31). Am J Rhinol 1995; 9: 297-306.

33. Sahlstrand-Johnson P, Ohlsson B, Von Buchwald C, Jannert M, Ahlner-Elmqvist M. A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. Rhinology 2011; 49: 420-428.

34. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngol Head Neck Surg 2007; 137: 555-561.

35. R Core Team (2013). R: A language and environment for statistical computing, Vienna, Austria: the R Foundation for Statistical Computing. ISBN 3-900051-07-0. Available from: www.R-project.org. Accessed March 2017.

36. Rakatomalala R. TANAGRA : un logiciel gratuit pour l'enseignement et la recherché. [TANAGRA: a free software for research and academic purposes]. Actes de EGC2005; RNTI-E-3: 697-702.

37. Selroos O, Kupczyk M, Kuna P, et al. National and regional asthma programmes in Europe. Eur Respir Rev 2015; 24: 474-483.

38. Tan DJ, Walters EH, Perret JL, et al. Age-of-asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. Expert Rev Respir Med 2015; 9: 109-123.

39. Oakley GM, Curtin K, Orb Q, Schaefer C, Orlandi RR, Alt JA. Familial risk of chronic rhinosinusitis with and without nasal polyposis: genetics or environment. Int Forum Allergy Rhinol 2015; 5: 276-282.

40. Hopkins C, Browne JP, Slack R, et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clin Otolaryngol 2006; 31: 390-398.

41. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Laryngoscope 2009; 119: 2459-2465.

Prof. Dr Claus Bachert
Upper Airways Research
Laboratory (URL)
Chief of Clinics ENT Department
University Hospital Ghent
De Pintelaan 185
9000 Ghent
Belgium

Tel: +32 (0)9 332 23 32
E-mail: claus.bachert@ugent.be

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 EPOS definition and all patients should have:	
	1. Inflammation of the nose and the paranasal sinuses characterised by 2 or more symptoms (1 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 (1 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; GALEN, Global Allergy and Asthma European Network; HIV, human immunodeficiency virus.