Clinical pheno- and endotyping of chronic rhinosinusitis

Griet VANDEPLAS

Promotor: Prof. dr. Claus Bachert

Masterproef voorgedragen in de master in de specialistische geneeskunde
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List of Abbreviations

AERD  Aspirin Exacerbated Respiratory Disease
AFS  Allergic Fungal Sinusitis
AR  Allergic Rhinitis
ARS  Acute Rhinosinusitis
BMH  Blank Medical History
CF  Cystic Fibrosis
COPD  Chronic Obstructive Pulmonary Disease
CRS  Chronic Rhinosinusitis
CRSsNP  Chronic Rhinosinusitis without Nasal Polyps
CRSwNP  Chronic Rhinosinusitis with Nasal Polyps
CT  Computed Tomography
ECP  Eosinophil Cationic Protein
ENT  Ear-, Nose-, Throat
EPOS  European Position Paper on Rhinosinusitis and Nasal Polyps
FEV1/FVC  Tiffeneau-Pinelli Index
FEV1  Forced expiratory volume in 1 second
FVC  Forced Vital Capacity
GALEN  Global Allergy and Asthma European Network
IFN-γ  Interferon-gamma
PND  Postnasal Drip
N  Number
SME  Small and Medium Enterprise
TGF-β  Transforming Growth Factor-beta
VAS  Visual Analogue Scale
Vs.  Versus
Yrs  Years
I. Abstract

**INTRODUCTION:** Chronic rhinosinusitis (CRS) is an inflammatory condition of nose and paranasal sinuses. It is subdivided in chronic rhinosinusitis without (or *sine*) nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) based on clinical grounds. Though very prevalent, a lot of questions about pathophysiology, clinical evolution, influence of the microbiome remain unanswered. In this masterthesis we tried to give a clear overview of the clinical course of disease in the two major subgroups, considering environmental exposures, symptoms, comorbidities and treatment.

**METHODS:** Our findings are based on the GALEN Sinusitis Cohort, a cohort including 869 patients from 9 European tertiary ENT clinics. Patients were included between April 2007 and December 2009.

**RESULTS:** Of all included patients 27.3% had CRSsNP, 51.2% had CRSwNP and 21.5% were controls. Results show cigarette use and alcohol exposure lead to higher symptom burden in CRS, and in a greater extend in CRSwNP patients compared to CRSsNP patients. CSRwNP have later onset of symptoms and of diagnosis. They have significantly more comorbid asthma and the asthma is later of onset and more often non-allergic. 30.2% of the patients suffers from allergic rhinitis (AR), 29.2% of CRSsNP vs. 33.6% of CRSwNP vs. 24.0% of control patients. Blocked nose is the most prevalent symptom in CRS. Patients with CRSsNP suffer significantly more from facial pain and pressure, headache and PND, whereas CRSwNP patients suffer significantly more from runny nose, sneezing and loss of smell. There is a correlation between the CT score and the CRS symptom burden, this was not found between the polyps score and the symptom burden. Treatment of CRS consists of medical and surgical treatment. Topical corticosteroids are the mainstay of CRS medical treatment. A third of patients underwent nasal surgery, also significantly more in CRSwNP patients.

**DISCUSSION:** Though at first sight CRSsNP and CRSwNP seem quiet alike, when we have a closer look we find significant differences between the two subgroups. CRSwNP patients seem to be more influenced by environmental exposure, have a higher symptom burden, more comorbid asthma and more use of medication and prior surgery.
II. Introduction

Chronic rhinosinusitis (CRS), being ‘the inflammation of nose and paranasal cavities’, is one of the most common chronic diseases. Overall prevalence of CRS in Europe is 10.9%, ranging from 6.9 to 27.1%, and prevalence seems to be increasing still (1). Comparable findings are supported by data from Canada and the USA where CRS affects approximately 12.5% of the population (2). The symptom burden and the impact on the quality of life and work productivity are often underestimated in CRS (3). CRS also has a significant impact on lower airway disease and on general health outcomes. Because of its direct and indirect medical costs and the high prevalence number it leads to a considerable socio-economic burden for the society (4, 5).

CRS is an umbrella term for different disease entities, with different underlying etiologies and pathophysiological mechanisms. On clinically observable characteristics, we differentiate CRS in two major subgroups, being chronic rhinosinusitis without (or sine) nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP). CRSsNP patients demonstrate a T(H)1 milieu, comprising high levels of interferon-gamma (IFN-\(\gamma\)) and transforming growth factor-beta (TGF-\(\beta\)) and histologic changes are defined by fibrosis, basement membrane thickening and goblet cell hyperplasia. CRSwNP, on the other hand, is characterized by a T(H)2-skewed eosinophilic inflammation with significantly higher levels of IL-5, IL-13, IgE, eotaxin, and eosinophil cationic protein (ECP) and edematous stroma with albumin deposition, pseudocysts and subepithelial and perivascular inflammatory cell infiltration (6, 7).

Although CRS is a highly prevalent condition, little is known about its pathogenesis. It is a multifactorial chronic inflammatory disorder with allergy, mucosal dysfunction, genetic and environmental factors and complex bacterial communities playing a role. Recently, using an extensive genealogical database linked to medical records, a large population-based study has attempted to characterize CRSwNP and CRSsNP, based on the genetic- and environment-associated risk of carrying the same diagnosis in relatives and spouses of patients with these conditions. A significant familial risk was confirmed in both CRSwNP and CRSsNP (8).

The diagnosis of CRS is made based on symptoms, nasal endoscopy and CT-scan. CRS symptoms are described by the EPOS 2012 (9) diagnostic criteria; being nasal obstruction, reduced sense of smell, facial pain or pressure and anterior or posterior nasal secretions. Rhinosinusitis becomes chronic when duration of symptoms exceeds 12 weeks in the past year.
In contrast to the histological diversity, the pattern of symptoms and signs is not very specific in patients with chronic sinus inflammation. Generally it is believed that CRSwNP have higher symptom scores with more olfactory dysfunction, whereas CRSsNP patients complain more of facial pain (10). However, these assumptions have not been proven in large clinical trials. It is currently not understood whether recurrent acute rhinosinusitis develops into chronic rhinosinusitis, which then possibly gives rise to polyp growth, or whether these disease entities develop independently from each other from the beginning. So far, nasal polyp formation in specific conditions such as cystic fibrosis (CF) and allergic fungal sinusitis (AFS) can be differentiated as disease entities, based on genetic defects in CF and a specific IgE-mediated immune response to local fungi in AFS, respectively. For the majority of chronic sinusitis cases however, classification awaits further insights into pathomechanisms and the introduction of appropriate disease markers. Also, frequent comorbidities are reported, like concomitant asthma, exacerbated respiratory disease (AERD), and allergic rhinitis (11). By characterizing CRS patients on the basis of clinical parameters, infectious agents, inflammatory mechanisms (chemokines, cytokines), and remodelling processes (growth factors), the term CRS can be further differentiated into smaller disease entities, referred to as endotypes, leading to more individualized treatment options with an expected advantage in morbidity.

The results of this work are based on the data from the GALEN Sinusitis Cohort, a large database with patient reported data from CRS patients, diagnosed according to the EPOS 2007 guidelines (12) and controls. The Global Allergy and Asthma European Network (GALEN)(13) is a network of excellence, covering 20 European countries, 60 collaboration centres, 27 research institutes and 2 SMEs (small and medium enterprises). Research by GALEN has provided insight into the epidemiology of CRS in Europe. However, the focus of the GALEN network is not CRS; therefore, the GALEN Sinusitis Cohort, was set up with the objective to study CRS and the natural history of the disease, treatment patterns, and clinical outcomes, quality of life and biomarkers. A recent GALEN Sinusitis Cohort publication describes a subgroup of CRS patients with available mucosal tissue samples, and provides an unbiased differentiation of CRS in clusters and inflammatory endotypes (14).

This masterthesis focusses on clinical parameters that influence the natural course of the disease in CRS. In asthma and allergic rhinitis extensive research is done to unravel the etiological
factors and natural history (15). In chronic rhinosinusitis, although a very common disease, little is known about the etiology and the factors leading to chronicity like genetic and environmental factors. There is also a paucity of accurate epidemiologic data on CRSsNP and CRSwNP, especially in European countries. We also focus on comorbidities, exposures and treatment, surgical or not.

III. Materials and Methods

Study design
It is a cross-sectional cohort study. The study protocol was approved by the Ethics Committees of all participating centres. Each centre was asked to recruit up to 100 fully characterized CRS patients and 25 control subjects. Prior to inclusion, in- and exclusion criteria were reviewed to ensure the patient’s suitability for inclusion in the study (see addendum 1). Written informed consent was obtained prior to any procedure being undertaken. The questionnaires were translated locally in each centre, and back translations were checked independently by the coordinating centre before final acceptance.

Patients
In 2006 this large multi-centre survey was initiated in the 9 participating European centres, 917 patients were included between April 2007 and December 2009. All patients were recruited in outpatient tertiary ENT (Ear, Nose, Throat) clinics. Male and female patients, aged 18-60 years, were eligible for entry to the study. Diagnosis of CRS was made by an ENT physician. The distribution of patients therefor does not necessarily reflect the distribution of the disease in the general population, but rather specific recruitment patterns of the respective clinics. Patients were subdivided in CRSsNP or CRSwNP according to the EPOS guidelines (12) and control patients. The control group was defined as an unmatched cohort of patients without CRS, with or without allergy symptoms, who were planning to undergo nasal surgery. Trauma patients and transnasal approaches for hypophysectomy and surgery for exophthalmia were also eligible as controls. 48 patients were excluded from further evaluation because of ‘other’ (eg. being allergic fungal sinusitis or antrochoanal polyp) or no diagnosis. All patients filled out a questionnaire, as did their treating physicians. Patients underwent nasal endoscopy, blood sampling, skin prick testing, sampling of nasal secretions and chest examination with lung function and spirometry. Computed
tomography (CT) scans of the sinuses were collected in case patients had a CT scan of maximum 12 months before the date of inclusion available. In case surgery was performed on a later time point, nasal tissue sampling was also performed.

Table 1: Participating centres with number of included subjects. Subdivision according to diagnosis, in chronic rhinosinusitis without nasal polyps (CRSsNP), chronic rhinosinusitis with nasal polyps (CRSwNP) and controls.

<table>
<thead>
<tr>
<th>Centres</th>
<th>CRSsNP N (%)</th>
<th>CRSwNP N (%)</th>
<th>Control N (%)</th>
<th>All N(%)</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Germany</strong> Charité - Universitätsmedizin Berlin</td>
<td>96 (40.5%)</td>
<td>24 (5.4%)</td>
<td>28 (15%)</td>
<td>148 (17.0%)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Belgium (Ghent)</strong> Ghent university Hospital</td>
<td>48 (20.3%)</td>
<td>50 (11.2%)</td>
<td>43 (23%)</td>
<td>141 (16.2%)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Poland</strong> Medical University of Lodz and Cracow</td>
<td>16 (6.8%)</td>
<td>95 (21.3%)</td>
<td>28 (15%)</td>
<td>139 (16.0%)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Spain</strong> Institut Municipal Investigacio Medica Barcelona</td>
<td>8 (3.4%)</td>
<td>100 (22.5%)</td>
<td>0</td>
<td>108 (12.4%)</td>
<td>10</td>
</tr>
<tr>
<td><strong>The Netherlands</strong> Academic Medical Centre Amsterdam</td>
<td>24 (10.1%)</td>
<td>61 (13.7%)</td>
<td>17 (9.1%)</td>
<td>102 (11.7%)</td>
<td>4</td>
</tr>
<tr>
<td><strong>Finland</strong> Helsinki University Central Hospital</td>
<td>0</td>
<td>59 (13.3%)</td>
<td>31 (16.6%)</td>
<td>90 (10.4%)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sweden</strong> Karolinska Institute Stockholm</td>
<td>28 (11.8%)</td>
<td>42 (9.4%)</td>
<td>18 (9.6%)</td>
<td>88 (10.1%)</td>
<td>10</td>
</tr>
<tr>
<td><strong>Belgium (Leuven)</strong> University Hospital Leuven</td>
<td>16 (6.8%)</td>
<td>8 (1.8%)</td>
<td>17 (9.1%)</td>
<td>41 (4.7%)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Great Britain</strong> Imperial College of Science Technology and Medicine London</td>
<td>1 (0.4%)</td>
<td>6 (1.3%)</td>
<td>5 (2.7%)</td>
<td>12 (1.4%)</td>
<td>2</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>237 (27.3%)</td>
<td>445 (51.2%)</td>
<td>187 (21.5%)</td>
<td>869 (100%)</td>
<td>48</td>
</tr>
</tbody>
</table>
Statistics
Patients’ data were collected on paper forms and then entered manually into a Microsoft Excel file at the respective study centre. The data were then transferred to Ghent University, where they were collated and merged into a single file comprising patient reported, clinician reported and biomarker data.

For data analysis SPSS (IBM SPSS Statistics version 22) was used. Statistical hypothesizes were based on Chi-squared test, independent sample t-test and Pearson correlation coefficient. P-values for clinical significance were based on a confidence interval of 95%.

IV. Results
Epidemiology
A total of 869 patients were included in the cohort. Mean age was 42.1 years. CRSwNP are older than CRSsNP patients (46.8 (SD 11.2) vs. 40.8 (SD 12.6) yrs). The gender distribution M/F was balanced (1.22 male to 1 female), 1.42 for CRSwNP, 0.96 for CRSsNP and 1.21 for controls. Since this is a European cohort study, the majority of patients (> 95%) was Caucasian. Of all included patients 27.3% had CRSsNP, 51.2% had CRSwNP and 21.5% were considered as controls. See table 2 for more demographic data.

Table 2: Patient characteristics. Subdivision according to diagnosis in CRSsNP, CRSwNP and controls.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency (%)</th>
<th>Diagnosis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>CRSsNP (%)</td>
<td>CRSwNP (%)</td>
<td>Control (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>116 (50.9)</td>
<td>112 (49.1)</td>
<td>157 (41.4)</td>
<td>222 (58.6)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>354 (45.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>432 (55.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age group</td>
<td></td>
<td>116 (50.9)</td>
<td>157 (41.4)</td>
<td>81 (45.3)</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>177 (22.5)</td>
<td>58 (25.4)</td>
<td>38 (10.0)</td>
<td>81 (45.3)</td>
</tr>
<tr>
<td></td>
<td>31-45</td>
<td>283 (36.0)</td>
<td>87 (38.2)</td>
<td>130 (34.2)</td>
<td>66 (36.9)</td>
</tr>
<tr>
<td></td>
<td>46-60</td>
<td>275 (34.9)</td>
<td>69 (30.2)</td>
<td>179 (47.1)</td>
<td>27 (15.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>52 (6.6)</td>
<td>14 (6.1)</td>
<td>33 (8.7)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Mean age (yrs)</td>
<td>42.1</td>
<td>40.6</td>
<td>46.8</td>
<td>34.3</td>
</tr>
</tbody>
</table>
### Exposure

#### Cigarette smoke

56.9% (448 patients) of included patients ever smoked, 37% of this subgroup (167 patients) are current smokers. Mean amount of pack years was 12.1, maximum amount 67.5. CRSsNP smoke more often compared to CRSwNP and controls, but this did not reach clinical significance. Of all patients who report a history of smoking, a significantly greater deal of CRSwNP patients stopped smoking (42.0% reduction compared to 31.4% in CRSsNP patients). Patients were asked to rate the symptom severity according to a visual analogue scale (VAS) of 0–10; with 0= no problem and 10= worst imaginable complaint; as recommended by the EPOS guidelines (12). In the CRSsNP group there was a higher symptom burden in the active smoking subgroup for general symptoms, blocked nose, pain, loss of smell, itching nose and ear, sneezing and headache, but these differences did not reach clinical significance. In the CRSwNP group the active smoking subgroup had more complaints for all questioned complaints except for epistaxis, but only blocked nose reached clinical significance (p=0.035).

#### Alcohol

Overall 41.9% of all patients reported to drink alcohol regularly (once a week or more). Patients were asked if they had the feeling alcohol intake worsened their upper airway complaints,
blocked nose, runny nose, postnasal drip (PND) and sneezing. 22.8% of patients had the feeling it does (12.9% of CRSsNP patients vs. 30.6% of CRSwNP patients), and this compared to 9.6% of control patients, this difference is clinically significant (p< 0.05). All of the symptoms worsened to a greater extent in the CRSwNP group compared to the CRSsNP group, however, the difference between the two groups was only significant for runny nose (p=0.036). The influence of alcohol intake was smallest in the control group.

Environmental exposure
66.2% of all patients lived in the city (32% report constantly passing cars). 13.1% in rural areas (37% of patients report never or seldom cars passing), and 20% in semi-rural areas; with no significant differences between the numbers of patients living in either of these areas among the three patient groups.

For all environmental and professional exposures, we see the highest exposure in the CRSwNP group, followed by the CRSsNP group and the control group.
33.2% is exposed to air-conditioning in the car or at the office, 50.0% from the exposed subgroup is in the CRSwNP group, 29.2% in the CRSsNP group, 20.8% in the control group.
26.8% is exposed to dust (eg. construction industry, cleaning, paper), 55.6% from the exposed subgroup is in the CRSwNP group, which is significantly more than 27.3% in the CRSsNP group, 19.4% in the control group. In the subgroup exposed to dust, we see significantly more severe complaints according to the VAS-scores for general symptoms, blocked nose, pain, runny nose, itching, itching throat and ears, sneezing and headache.
11.4% is exposed to gasses (eg. exhaust gasses, solvents), 55.4% from the exposed subgroup is in the CRSwNP group, 26.5% in the CRSsNP group, 18.1% in the control group.
10.0% is exposed to fumes (eg. cigarettes, traffic), 61.1% from the exposed subgroup is in the CRSwNP group, which is significantly more than 20.8% in the CRSsNP group, 18.1% in the control group. Here we see significantly more complaints of itching throat in the exposed subgroup, mainly in the CRSwNP subgroup (p=0.040).
10.0% is exposed to extreme temperatures (eg. cook, bakery), 50.8% from the exposed subgroup is in the CRSwNP group, 25.4% in the CRSsNP group, 23.8% in the control group. Here we also see significantly more complaints in the exposed subgroup for general symptoms, blocked nose, itching and itching throat, sneezing and headache, also mainly in the CRSwNP subgroup.
7.3% is exposed to allergens (e.g. animal dander, latex), 63.6% from the exposed subgroup is in the CRSwNP group, 22.7% in the CRSsNP group, 13.6% in the control group.

Onset of disease
Mean age of diagnosis of CRS (CRSsNP and CRSwNP) is 34 years. Age of onset of symptoms and the age of CRS diagnosis is significantly earlier in CRSsNP group compared to CRSwNP group. CRSwNP patients have longer symptom duration (12.8 (SD10.5) vs. 9.8 (SD 10.5) yrs), are older (46.8 (SD 11.2) vs. 40.8 (SD 12.6) yrs). 50% of the patients in both the CRSsNP and the CRSwNP group have their diagnosis of CRS in the same year the symptoms started, but mean delay between symptom appearance and diagnosis is more than 2 years.

Table 3: Age of onset and time lags in years, compared between CRSsNP and CRSwNP. P-values in bold are significant.

<table>
<thead>
<tr>
<th></th>
<th>CRSsNP</th>
<th>CRSwNP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset of symptoms</td>
<td>30.17</td>
<td>33.64</td>
<td>0.004</td>
</tr>
<tr>
<td>Age of diagnosis CRS</td>
<td>32.47</td>
<td>35.29</td>
<td>0.018</td>
</tr>
<tr>
<td>Time lag between symptoms and diagnosis of CRS</td>
<td>2.52</td>
<td>2.02</td>
<td>0.351</td>
</tr>
<tr>
<td>Age of asthma diagnosis</td>
<td>24.84</td>
<td>33.23</td>
<td>0.002</td>
</tr>
<tr>
<td>Time lag between asthma diagnosis and CRS diagnosis</td>
<td>5.22</td>
<td>1.86</td>
<td>0.151</td>
</tr>
</tbody>
</table>

Figure 1: Timeline of start of the complaints compared to time of diagnosis. Blue square: CRSsNP, red square: CRSwNP, yellow square: controls.

Symptoms
Patients were asked to rate their symptom severity according to a visual analogue scale (VAS) of 0–10; with 0= no problem and 10= worst imaginable complaint; as recommended by the EPOS guidelines (9, 12). A VAS-score of 0-3 represents mild symptoms, >3-7 represents moderate...
symptoms, > 7-10 severe symptoms. A VAS-score of >5 is considered the threshold above which the quality of life is impacted (16). The different symptoms were: general symptoms, runny nose, blocked nose, facial pain and pressure, headache, PND, loss of smell, itching of nose, ear or throat, sneezing and epistaxis. The general symptom VAS-score for overall rhinosinusitis was high (6.40 vs. 6.81) as was the score for blocked nose (6.19 vs. 6.68) for CRSwNP and CRSsNP. In the CRSsNP group, patients suffer significantly more from facial pain and pressure (4.02 (SD3.24)), headache (5.17 (SD 3.45)) and PND (5.43 (SD 3.24)). In the CRSwNP group, they suffer significantly more from runny nose (4.91 (SD 3.25)) and loss of smell (6.41 (SD 3.71)). This symptom burden is independent from the allergic status of the patient. The symptoms of facial pain or pressure and headache were present significantly earlier in the history of the disease in the CRSsNP group (p 0.011 and p 0.005). Loss of smell is mentioned significantly earlier in the history of the disease in the CRSwNP group (p< 0.001).

CRS patients were asked to think back what they define as their first sign of CRS. In the CRSwNP group, 35.0% considers a common cold as the first sign of CRS, in the CRSsNP group 37.3% considers headache and facial pressure as the first sign. In case complaints started with loss of smell, they developed to nasal polyps in 77% of cases, in case complaints started with headache, 56.4% developed to CRSsNP.

**Figure 2:** Start of CRS. ARS: acute rhinosinusitis; BMH: I had a blank medical history before it started; LoSmell: loss of smell; Head: headache and facial pressure; Cold: common cold.
Patients was asked to score seven CRS symptoms (blocked nose, runny nose, loss of smell, PND, facial pain or pressure, headache and episodes of acute rhinosinusitis) on duration, order and frequency. 43% of CRS patients reported all seven symptoms. Duration of the symptoms was longer in the CRSwNP group and this for all the symptoms, and this difference reached clinical significance for all symptoms except for headache.

**Table 4: Difference in order of development of symptoms between CRSsNP and CRSwNP.**

<table>
<thead>
<tr>
<th></th>
<th>CRSsNP</th>
<th>CRSwNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>blocked nose (49.0%)</td>
<td>blocked nose (53.6%)</td>
</tr>
<tr>
<td>Second</td>
<td>facial pain or pressure (26.7%)</td>
<td>runny nose (30.1%) or facial pain or pressure (17.2%)</td>
</tr>
<tr>
<td>Third</td>
<td>runny nose (26.4%) and PND (20.0%)</td>
<td>loss of smell (24.1%) and PND (21.9%)</td>
</tr>
<tr>
<td>Fourth</td>
<td>loss of smell (23.1%) or headache (22.0%)</td>
<td>headache (17.8%)</td>
</tr>
<tr>
<td>Last</td>
<td>acute sinusitis (25.7%)</td>
<td>acute sinusitis (25.7%)</td>
</tr>
</tbody>
</table>

**Figure 3: Frequency of the symptoms in the last month.** Scores: 0= not at all, 1=<1/week, 2=≥1/week, 3=1/day, 4=continuously. *shows clinical significance.
In the last month before filling out the questionnaire, CRSwNP patients experienced significantly more runny nose and loss of smell, whereas CRSsNP experienced more PND and headache. 40% of the CRS patients reported blocked nose to be continuous over the last month.

**Comorbidities**

Asthma is, according to the questionnaire, diagnosed in 33.3% of included patients: 20.2% of the CRSsNP patients, in 49.6% of the CRSwNP patients (significantly more p<0.0001) and in 13.6% of control patients. In the CRSsNP group, asthma was diagnosed before the diagnosis of CRS in 75%, in CRSwNP group, asthma was diagnosed before the diagnosis of CRS in 60%.

**Figure 4: Score 0 on the X-axis means diagnosis of asthma and CRS were on the same time. Negative scores (white area) mean the diagnosis of CRS is after diagnosis asthma, positive scores (grey area) means diagnosis of CRS is before asthma. (1= CRSsNP, 2=CRSwNP)**

CRSwNP have significantly later onset of asthma compared to CRSsNP (33.23yrs vs. 24.84yrs, p=0.002). In both CRSsNP and control groups the majority of patients had early onset asthma, starting before the age of 20 years (43.2% and 50.0%, respectively), whereas in the CRSwNP group, the majority of patients (50.0%) had late onset asthma, starting after the age of 40 years.
Figure 5: The age of onset of asthma in both CRSwNP and CRSsNP in different age groups.

FEV1/FVC (FEV1%) is the ratio of the Forced expiratory volume in 1 second (FEV1) to the forced vital capacity (FVC), also called the Tiffeneau-Pinelli Index. In healthy adults this should be approximately 70–85% (declining with age). In obstructive diseases (asthma, COPD, chronic bronchitis, emphysema) a reduced value (<80%) of the FEV1/FVC is seen. Among the patients with ‘no-asthma’, as reported in the questionnaire, 44.4% (N=71 out of 160), had a FEV1/FVC ratio of < 80%. Of these patient subgroup, 37.2% (N=16) was a CRSsNP patient, 55.2% (N=48) a CRSwNP patient and 23.3% (N=7) a control patient.

Figure 6: FEV1/FVC ratio A. among the total group of included patients. B. among the group who reported ‘no asthma’ in the questionnaire.
30.2% of the patients were diagnosed as allergic rhinitis (AR) sufferers, 29.2% of CRSsNP vs. 33.6% of CRSwNP vs. 24.0% of control patients. The age of diagnosis of CRS and asthma was significantly lower in the subgroup with allergic rhinitis. In both CRSsNP and CRSwNP, there were significantly more asthmatics in the subgroup with AR compared to the subgroup without AR (CRSsNP 31.7% compared to 14.9%, p= 0.008 and CRSwNP 77.2% compared to 34.8% p<0.001). Whereas asthma was the most frequent comorbidity in CRSwNP, contact allergy was significantly more present in CRSsNP (15.1% in CRSsNP compared to 5.2% in CRSwNP and 9% in controls).

4.4% of all patients mentioned aspirin exacerbated respiratory disease (AERD) and this was more prevalent in CRSwNP versus CRSsNP and control patients (7.4% vs 1.3%, controls 1.1%, p<0.0001). The presence of AERD was based on the physician’s questionnaire; a confirmation by aspirin challenge was not done. 90.9% of the aspirin intolerant patients in CRSwNP had asthma, a triad better known as Samter’s Triad (p<0.001); in the CRSsNP group, 66.7% of aspirin intolerant patients (being only 3 out of 218 patients) had asthma (p= 0.104).

**Polyp score**
Each enrolled patient underwent nasal endoscopy by an ENT specialist. The endoscopic findings for each patient were described clinically according to the Nasal Polyp Score: polyps were scored on a scale of 0-3 for each nostril (with 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 to 6 for both nostrils.

Mean polyp score was 1.61 on the left side and 1.57 on the right side, with a mean total polyp score of 3.18. 12.3% of patients have a polyp score between 4 and 6. A Pearson correlation coefficient was calculated to evaluate a correlation between the polyp score and the total symptom score as indicated with the VAS-score, but it couldn’t confirm a significant correlation. We do see higher VAS-scores for blocked nose and loss of smell in higher polyp scores.

**CT scores**
In case a recent CT-scan of maximum 12 months old was available for a patient, this was scored by the ENT specialist according to the Lund-Mackay CT scoring system (17). The maxillary sinus, anterior ethmoid, posterior ethmoid, sphenoid and frontal sinus were each scored on a scale.
of 0-2; with 0= no abnormalities, 1= partial opacification, and 2= complete opacification. The osiomeatal complex was scored on a two-point scale of 0 and 2; with 0= not occluded and 2= occluded. The scores for both the left and right side were added to provide a total CT-scan score of 0-24 (0-12 per side).

60% of the patients had an appropriate CT scan available. Mean Lund-Mackay score 8.32 in the CRSsNP subgroup and 14.15 in the CRSwNP subgroup. As expected, a higher CT score was related to a higher polyp score. The score was significantly worse in the CRSwNP group compared to the CRSsNP group, and this for all sinuses separate as well as for the total score (p<0.0001).

Table 5: Lund Mackay score for CRSsNP and CRSwNP subgroups, both sides and total.

<table>
<thead>
<tr>
<th>Lund Mackay score</th>
<th>CRSsNP</th>
<th>CRSwNP</th>
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<tbody>
<tr>
<td>- Right</td>
<td>4.20</td>
<td>7.11</td>
</tr>
<tr>
<td>- Left</td>
<td>4.13</td>
<td>7.01</td>
</tr>
<tr>
<td>- Total</td>
<td>8.32</td>
<td>14.15</td>
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The maxillary sinus was oppacified most, followed by the anterior ethmoid, posterior ethmoid, osteomeatal complex, frontal sinus and the sphenoid sinus was less oppacified.

We also calculated a Pearson correlation coefficient, there was a significant correlation between the total Lund-Mackay score in CRS patients and the VAS score for general symptoms score as indicated with the VAS-score (Pearson correlation 0.112, p=0.26) and between the total Lund-Mackay score and the sum of the different VAS-scores (Pearson correlation 0.111, p=0.29). In the CRSwNP subgroup, the VAS-scores for loss of smell, runny nose and blocked nose increased with increasing CT scores. In CRSsNP patients this trend was not observed.

Treatment
Overall 74.4% of patients have ever taken medication for sinus treatment, 28.8% of patients have taken 4-8 medications. 51.5% of CRS patients (CRSsNP + CRSwNP) is currently taking medication, but CRSwNP patients were more likely to be treated currently than CRSsNP patients (64.1% vs. 28.2%). Mainstay of treatment was intranasal corticosteroids; with 92.6% of CRS patients currently using these, compared to 13.3% using oral corticosteroids, 14.8% antihistamines, 13.7% antibiotics, and 21.9% other medication for nasal pathology (montelukast, NSAID, etc).
When we compare the CRSwNP to the CRSsNP group, all medication was taken more frequently by CRSwNP except for antibiotics. CRSsNP more often received antibiotics (30.6% vs. 9.7%, P=0.003), antibiotics also demonstrate greater efficacy in CRSsNP. CRSwNP patients more often received oral corticosteroids: 52% of CRSwNP ever received oral corticosteroids, compared to 22% of CRSsNP patients, 15.5% of CRSwNP patients is currently receiving oral corticosteroids compared to 4.1% of CRSsNP patients.

Patients were asked to score the efficacy of the medication ranging from 0 (not having any effect) to 3 (a lot better for a longer period). Corticosteroids, oral as well as nasal were perceived as having a good efficacy in both groups, efficacy scores were highest for oral corticosteroids in both CRSwNP (2.1) and CRSwNP (1.7). Nasal corticosteroids scored 1.9 in CRSwNP and 1.4 in CRSsNP.

36.4% of the patients previously had nasal surgery, 46% in the CRSwNP group, 23% in CRSsNP group and 5% in the control group. Some patients had more than one previous sinus operation, mean number of surgery is 1.6 in CRSsNP and 2.5 in CRSwNP. In the latter subgroup 23.4% of subjects underwent 4 surgeries or more. 40% of patients undergo surgery in the same year of diagnosis. Mean time lag to surgery was shorter in CRSsNP (0.14 years) as compared to CRSwNP (0.87 years).

V. Discussion

CRS is a heterogeneous group of inflammatory diseases of the nose and paranasal cavities, subdivided in two major subgroups, CRSsNP and CRSwNP. Histologically and in the inflammatory pathways we see clear differences between the two subgroups, but clinically both seem quiet alike. A recent GALEN study performed a cluster analysis on the subgroup of patients of the GALEN Sinusitis Cohort who had sinus tissue available. The patients were clustered based on their biomarker. Ten clusters were created, representing different inflammatory endotypes which largely correlated with phenotypes and further differentiated them. It makes us conclude that inflammation in CRS is more diverse than previously assumed. The goal of the clusters is to be guidance in predicting asthma comorbidity, recurrence after surgery and response to new
targeted drugs (14). In this masterthesis we tried to differentiate both subgroups based on symptoms and clinical course and compare them to controls.

Data are based on the GALEN Sinusitis Cohort. The GALEN Sinusitis Cohort is the world’s largest database of patients with CRS. In 9 large tertiary clinical centres throughout Europe, CRS patients were included and categorized as CRSsNP and CRSwNP based on EPOS criteria (9, 12). A total of 682 CRS patients were included for analysis. Furthermore, a group of 187 control patients, undergoing nasal surgery but with no medical history or symptoms of any form of CRS, was primarily employed as a reference for comparison with these CRS subgroups. The cohort was set up to define the different CRS entities according to the symptoms, the clinical course of the disease, the quality of life, the treatment, etc. Data are based on questionnaires filled out by the patients and their physicians as well as on objective observations like CT scans, lung function tests, etc.

When we resume our results, we see an influence of different environmental factors which might play a role in the complex pathophysiology of CRS. Smoking is a known risk factor for development of CRS (1) and our data show that active smokers with CRS tend to have more severe complaints compared to non-smokers, though not clinically significant. Alcohol intake worsens symptoms of CRS to a greater extend in the CRSwNP group compared to the CRSsNP group, mainly for running of the nose. The influence of alcohol on upper respiratory reactions is known to be greater in CRS patients compared to healthy controls (18). Environmental factors are more complex, our data describe higher exposures in the CRSwNP group, followed by the CRSsNP group and the control group, though we can discuss about the role of these factors as part of the etiology of the disease, or the fact that polyp patients are more sensitive to environmental factors. The influence of environmental factors in CRS is confirmed in a previous study of Oakley, who concluded that spouses of CRSsNP patients, who likely share environmental circumstances but no genetic factors, exhibited a 2-fold increased risk of developing CRSsNP. No increased risk was observed in spouses of CRSwNP patients (8).

There is quiet some overlap between both subgroups, CRSsNP and CRSwNP. When we look for the differences, we see CRSwNP patients are generally older male patients. In CRSwNP symptoms as well as diagnosis are present at later age compared to CRSsNP, also comorbid asthma tends to
be at later onset in the CRSwNP subgroup. CRSwNP patients have a longer symptom duration and have a higher proportion of previous surgery compared to CRSSNP patients. 40% of patients with CRS suffer from blocked nose, the subgroup with CRSSNP suffers significantly more from facial pain and pressure, headache and PND, whereas CRSwNP patients suffer significantly more from runny nose, sneezing and loss of smell. These observations were also described in earlier publications (10). We don’t see a correlation between the polyp score and the gravity of the symptoms, but for the CT-score we see the higher symptom scores for loss of smell, runny nose and blocked nose with increasing CT-score in the CRSwNP group. Asthma is very prevalent in CRS. This was also shown in a recent Europe-wide epidemiologic study on the prevalence of CRS. They showed asthma (early as well as late onset) was strongly associated with CRS in men, women and in all age groups. But the patients with CRS and no allergic rhinitis report more late-onset asthma (19). In our data 50% of the CRSwNP subgroup reports comorbid asthma and asthma is generally later of onset and more frequent non-allergic compared to the CRSSNP subgroup. Following asthma, the most prevalent comorbidity in CRS is allergic rhinitis. The CRSwNP subgroup also suffers significantly more from aspirin intolerance. There is a lot of medication use. Mainstay of treatment is nasal corticosteroids, which is used by almost all CRS patients (92.9%) as prescribed by the EPOS guidelines (9). In CRSSNP we see more antibiotic use, in CRSwNP more oral corticoid use. A lot of CRS patients underwent sinus surgery, we also see more surgery in the CRSwNP subgroup, even leading tot almost 25% undergoing more than four operations. Since this is a patient based questionnaire though, we don’t exactly know if it considers real endoscopic sinus surgery or minor invasive surgery like polypectomies. This study also has some limitations. In particular, the cohort was not designed to gather epidemiologic estimates and all patients were included in outpatient hospital setting in the random order of presentation. The patient distribution therefore does not necessarily reflect the distribution of the diseases in the general population, but rather specific recruitment patterns of the respective clinics. For example, in general population we see prevalences of CRSwNP of 1-4% (20), whereas in our cohort more than 50% of included patients had nasal polyps. Moreover, the study centres were large tertiary centres, which may possibly lead to an inclusion bias of patients with higher disease burden and more severe cases. Another possible bias is that more severe cases are more likely to participate in a clinical study.
CRS subjects were allocated to the subgroup CRSsNP or CRSwNP during office-based endoscopy. The clinical differentiation might be unclear in some cases of beginning nasal polyposis, it has been shown that in cases of middle turbinate–confined polypoid edema the phenotype might not be clear-cut during office-based endoscopy, still early-stage nasal polyps already show eosinophilic inflammation (21). Also, control patients were patients undergoing sinus surgery such as septoplasty or septorhinoplasty and although they reported no medical history or symptoms of any form of CRS, they might have more nasal symptoms than the general healthy population. Finally, as the data were collected retrospectively and relied on patient reports, they could be subject to a recall bias; which in a questionnaire-based study has been shown to be a systematic error caused by differences in the accuracy or completeness of the recollections retrieved (“recalled”) by study participants regarding events or experiences from the past.

VI. Conclusions and future perspectives

With the data of this large European CRS cohort we made an overview of the clinical differences between CRSsNP and CRSwNP and we can conclude both subgroups are comparable in many ways but CRSwNP patients seem to have higher symptom burden, more medication use and more prior surgery. They also have more comorbid and later onset of asthma.

It would be interesting to look further into blood results, nasal secretions and nasal tissue to see how differences in cytokine spectrum and genetic factors translate into differences in symptom burden. If we have a clearer view on all these clinical, histological, immunological and genetic factors this could lead us in taking therapeutic decisions like prognosis of surgery, use of new targeted drugs like monoclonal antibodies, etc.
VII. References

Addendum

**Addendum 1: Cohort inclusion and exclusion criteria**

<table>
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<th>Inclusion criteria</th>
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<tr>
<td><strong>For all subjects:</strong></td>
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<tr>
<td>1. The subject understands the study procedures and agrees to participate by signing the consent form.</td>
</tr>
<tr>
<td>2. The subject is male or female between 18 and 60 years of age.</td>
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<tr>
<td>3. Except from 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.</td>
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### Diagnosis of CRS:

The diagnosis of CRS (with or without nasal polyps, including fungal disease, cystic fibrosis, etc.) is based on the EPOS$^4$ definition and all patients should have:

1. Inflammation of the nose and the paranasal sinuses characterized by two or more symptoms:
   - a. Blockage/congestion
   - b. 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:
     - Polyps
     - Mucopurulent discharge from middle meatus
     - Oedema/mucosal obstruction primarily in middle meatus

3. And

   - a. CT-changes: Mucosal changes within the osteomeatal complex and/or sinuses
   - b. Duration of the disease: >12 weeks of symptoms
   - c. No complete resolution of the symptoms

NB: Patients with antrochoanal polyps were excluded.

### Controls

Controls 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 transnasal approaches for hypophysectomy and surgery for exophtalmia could be included as controls as well. Patients
with allergy (sensitization 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 two weeks) are not allowed to participate. |
| | 2. The subject had former functional endoscopic sinus surgery (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 breast feeding. |
| | 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, 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. Inhalation steroids for asthma are permitted but should be documented in the questionnaires.